Biology for Physicians: Human Genetics — Inheritance in Human Beings

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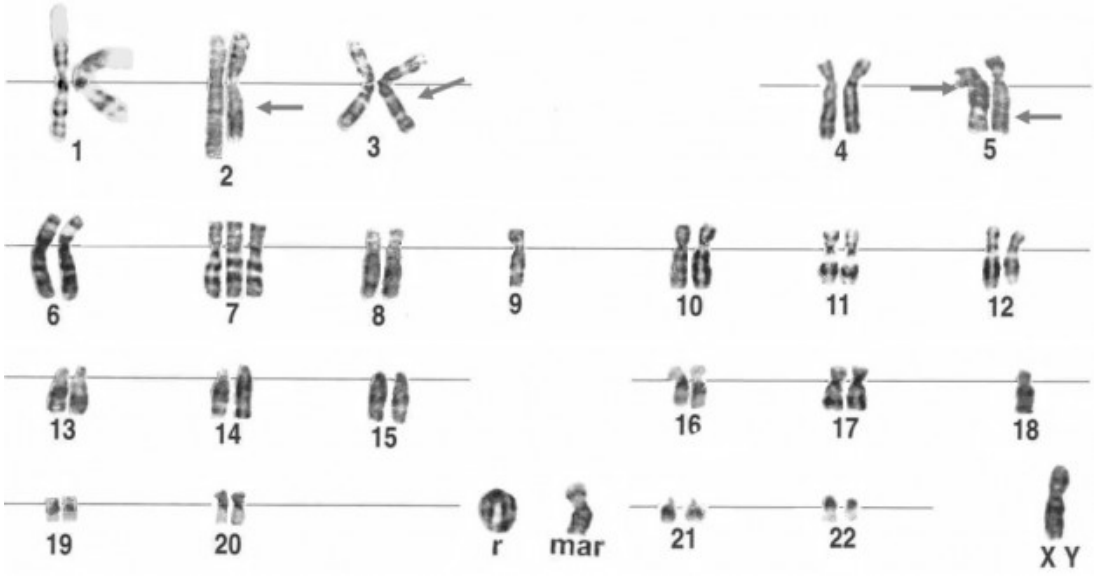
"This is genetic!" Which diseases are inherited as an autosomal dominant trait and which as an X-chromosomal recessive trait? What is the purpose of our gonosomes? How do you calculate a risk for an inheritance? What do you know about genomic imprinting and the inheritance of blood types? In this article, we offer you everything you need to know about human genetics including the most important facts and genealogical trees of major genetic diseases.

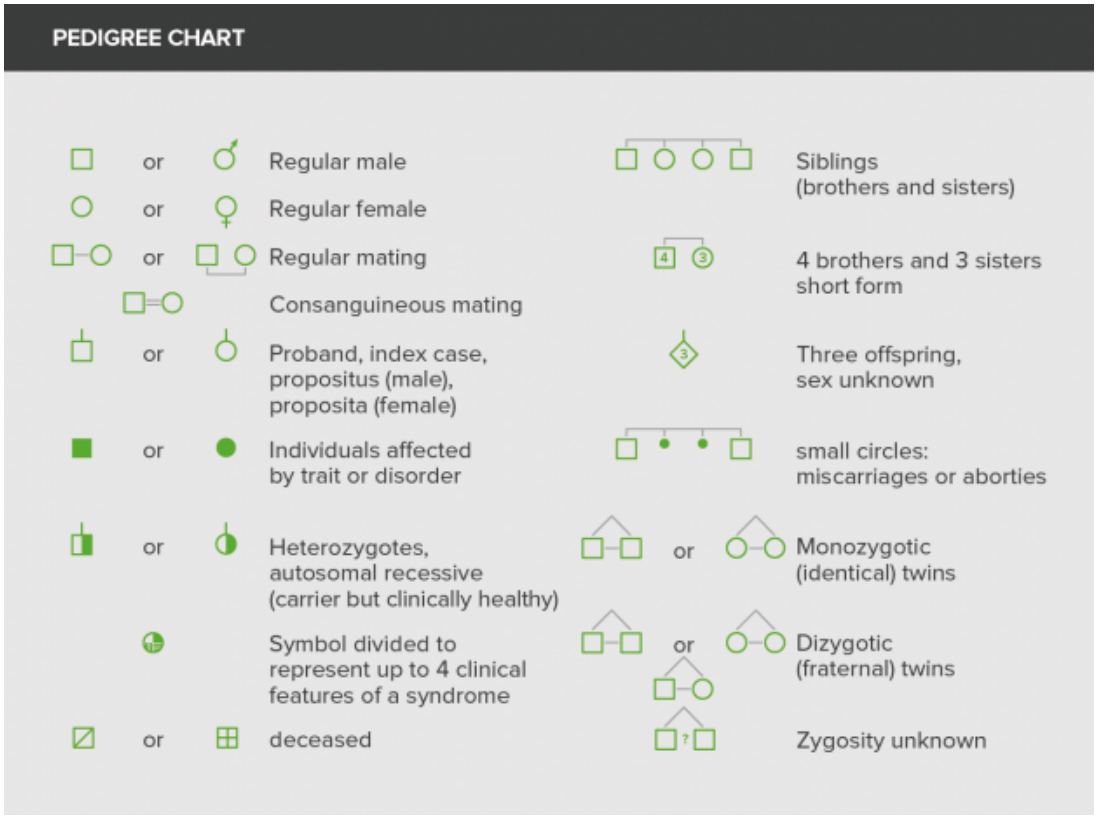


Human Genetics: What is It?

Human genetics deals with the genetic constitution of human beings. In this area, medical diagnostics and molecular biological research work closely together. In pre-clinic semesters, the basic concepts, different inheritance traits, and pedigree analyses are the most important concepts to learn.

Study tip: For each mode of inheritance, take a close look at the genealogical tree of a typical disease and try to understand why a person is diseased and what the individual phenotypes and genotypes look like.

Symbols of genetics



Symbols of genetics. Image by Lecturio

Autosomal Inheritance: Dominant and Recessive

In autosomal inheritance, genetic information is located on chromosomes 1–22. Thus, inheritance is not gender-specific.

Autosomal Dominant Inheritance

If traits are inherited as autosomal dominant, they may be expressed in the heterozygous or homozygous state. An organism can be **homozygous** dominant if it carries **2 copies** of the same dominant allele, or **homozygous** recessive if it carries 2 copies of the same recessive allele. **Heterozygous** means that an organism has **2 different alleles of a gene**. Statistically, the most frequent distribution is the inheritance from 1 parent to half of the children (in cases of complete penetrance).

An **allele** is 1 of the possible forms of a gene. Most genes have 2 **alleles:** a **dominant allele and a recessive allele**. If an organism is heterozygous for that trait or possesses 1 of each **allele**, **then the dominant trait is expressed.**

Important: Healthy persons do not carry the trait. In autosomal dominant diseases, individuals who carry the trait are always diseased.
Probability of offspring expressing the dominant trait: 50%–100%.

Examples of Combination

- 1 parent is heterozygous for the trait: **A**a x aa = 50% **A**a + 50% aa
- 1 parent is homozygous for the trait: **AA** x aa = 100% **A**a

If the trait is the trigger for disease, homozygous individuals are often affected more severely than heterozygous ones. Autosomal dominant diseases can be tracked over

generations, since, in every generation, persons are diseased. (Exceptions include **achondroplasia** and **Marfan's syndrome**, which are due to de novo mutations.)

Autosomal Dominant Diseases

- **Polydactyly** (more fingers than usual)
- **Brachydactyl** (unusually short fingers)
- **Ectrodactyly** (lobster-claw hand or split foot)
- **Achondroplasia** (disproportioned dwarfism): Disturbed cartilage formation occurs. The absence of growth plates in the bones results in disproportioned dwarfism with a normal length of the torso and markedly short extremities. In 80% of cases, a de novo mutation is the cause.
- **Marfan's syndrome**: Mutation in the gene for fibrillin with disturbed synthesis of connective tissue.
- **Huntington's disease**: Causes are triplet (CAG) repeat expansions, which have destructive consequences for the neurons of the basal ganglia in the brain. Penetration depends on the number of triplet repeats: With > 60 CAG triplets, Huntington's disease already occurs at a young age.

Hint: Autosomal dominant diseases are often associated with a dysfunctional structure of cells and tissues.

Autosomal Recessive Inheritance

In autosomal recessive inheritance, the carrier must be homozygous for the trait to be inherited. Heterozygous people act as carriers but they do not express the respective phenotype. A phenotypically diseased person must inherit the recessive gene from both parents.

Examples of Combination

- If 1 parent is homozygous and healthy and the other parent is heterozygous for the trait, all children will be phenotypically healthy, but half will be carriers: A**a** x AA = 50% A**a** + 50% AA
- If both parents are heterozygous for the trait, 25% of the children will be diseased, 50% will be heterozygous carriers, and 25% will be homozygous and healthy: A**a** x A**a** = 25% **aa** + 50% A**a** + 25% AA

In pedigrees, autosomal-recessive diseases are not as easy to track as autosomal-dominant diseases. Several generations can not exhibit the trait before someone becomes diseased again. The offspring from marriages between related persons are affected more often, as the chance that both parents carry the recessive gene is increased.

Autosomal Recessive Diseases

- **Albinism**: Disturbed biosynthesis of melanin due to absent tyrosine hydroxylase. Results in lack of pigments: very white skin and hair, and high sensitivity to UV light.
- **Phenylketonuria**: Phenylalanine cannot be degraded due to lack of phenylalanine hydroxylase; as well, it accumulates in the organism. Consequences are very severe psychomotor retardations. Treatment is a diet low in phenylalanine.
- **Cystic fibrosis**: Trinucleotid deletions on chromosome 7, which codes for the

CFRT transporter (chloride transporter). Chloride ions cannot be transported and added to secretions, which remain viscous with severe clinical consequences for affected patients (among other things, recurrent respiratory infections, and malabsorption disorders). All exocrine glands are affected.

- **Deaf-muteness**

An autosomal recessive trait that does not represent a disease is blood type 0.

Hint: Autosomal recessive inheritance is the common inheritance mode for metabolic diseases.

Gonosomes: Important Facts about Chromosomes X and Y

In the human set of chromosomes, 1 pair of chromosomes is not homologous: the gonosomes X and Y. They determine the genetic gender.

The following table provides an overview of the properties and functions of the Y and X chromosomes.

Y chromosome	X chromosome
Little information (location of very few genes)	Rich in information (regulation of many functions of the organism)
Most important gene of the Y chromosome; determines gender (**sex-determining region of Y: SRY**)	Double dose of X chromosomal localized genes
SRY induces the development of the testes and production of testosterone	**Dosage compensation mechanism**: Compensation through irreversible inactivation of 1 of the 2 X-chromosomes >> Barr bodies (sex chromatin) at the edge of the nucleus
Sexual maldevelopments: XX male: During meiosis, the SRY gene is translocated to other chromosomes >> male phenotype despite missing Y chromosome, sterility. **XY woman**: SRY inactivation due to mutation >> secondary gender development does not occur, possible infertility	**Genetic mosaics**: In 50%, the maternal X chromosome is active in the female organism; in the other 50%, the paternal X chromosome is active.
Testicular feminization: a defective receptor for testosterone >> XY person with female phenotype, sterility	Reversion of inactivity in the germline

Gonosomal Modes of Inheritance

Traits bound to the gonosomes are present if the respective trait is located on 1 of the 2 gender chromosomes.

X-Linked Dominant Inheritance

The X-linked dominant inheritance trait is a very rare inheritance mode.

Examples of Combination

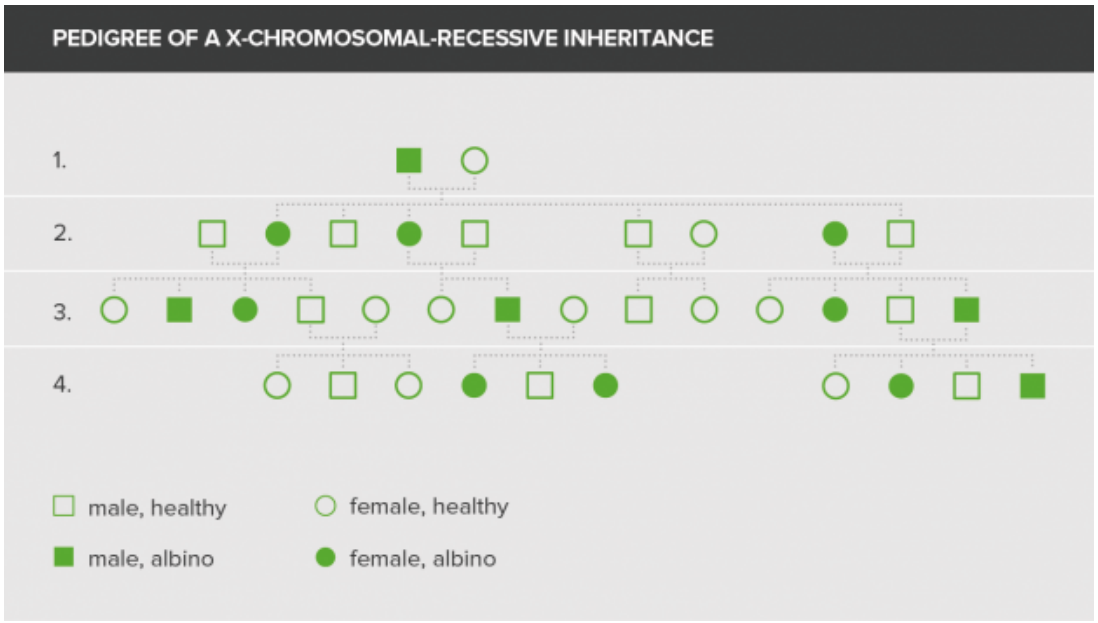
- Father is a carrier of the mutated allele: All sons are healthy, all daughters are diseased. Xy x xx = 50% xy + **50% X**x
- Mother is a carrier of the mutated allele: 50% of the sons, 50% of the daughters are diseased. xy x Xx = **25% X**y + 25% xy + **25% X**x + 25% xx

X-Linked Dominant Diseases

- **Hypophosphatemia** (vitamin D–resistant rickets)
- **Rett's syndrome**
- **Alport's syndrome**

X-Linked Recessive Inheritance

The X-linked recessive inheritance mode occurs far more frequently. Men are considerably more likely to be affected than women.



Pedigree of an X-chromosomal-dominant inheritance. Image b Lecturio

Examples of Combination:

- If the father has the mutated allele, he is phenotypically diseased and passes this allele to his daughters. If the mother is homozygous and healthy, her daughters will only become carriers. The father's allele is not given to the sons, who are neither diseased nor carriers: **x**Y x XX = 50% **x**X + 50% Xy
- If the mother is a heterozygous conductor, 50% of her sons will be diseased and 50% of her daughters will become carriers: XY x X**x** = **25% x**Y + 25% XY + 25% **x**X + 25% XX
- If the man is diseased and the woman is a carrier, 50% of the sons and 50% of the daughters will become diseased. The other half of the daughters will become carriers: **x**Y x X**x** = 25% **x**Y + 25% XY + 25% X**x** + 25% **xx**

X-Linked Recessive Diseases

- **Hemophilia A** (factor VIII deficiency) and **hemophilia B** (factor IX deficiency)
- **Dyschromatopsia** (heterogonia)
- **Duchenne muscular dystrophy**

A very famous genealogical tree showing an X-linked recessive disease is the family tree of Queen Victoria of England. The royal family suffered from hemophilia.

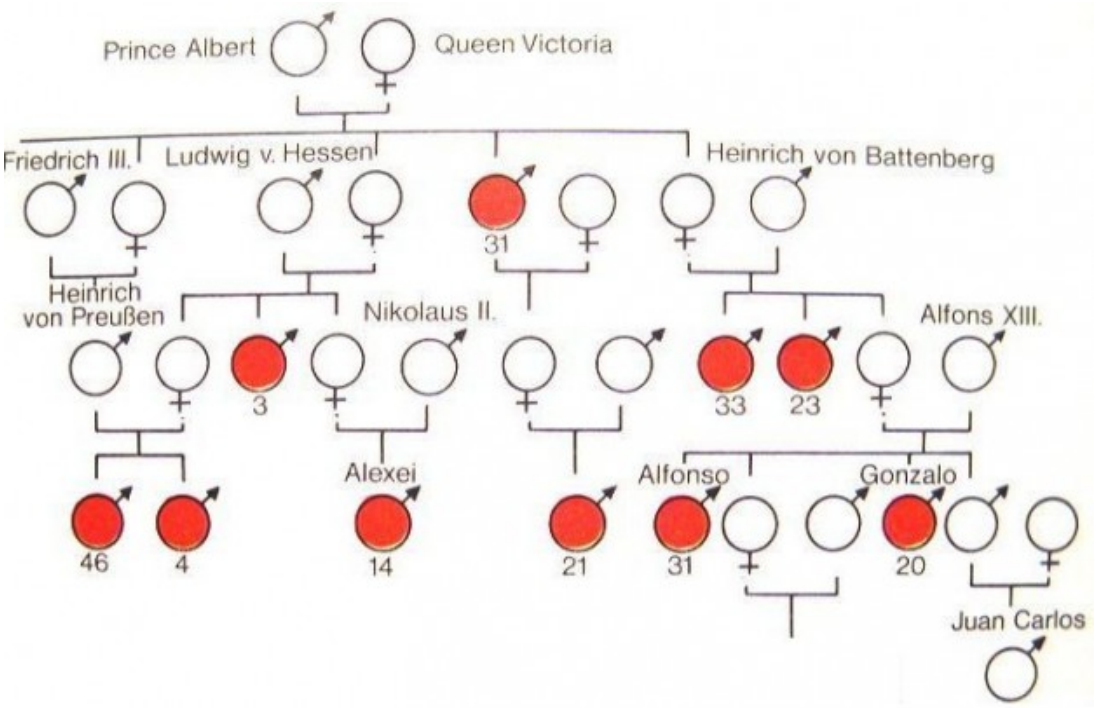


Image: “Inheritance of hemophilia” by Caro1409. License: CC BY-SA 3.0

Inheritance of Blood Types

There are 20 different blood-type systems. The most important ones are the **AB0 system**, the **MN system**, and the **Rh system**.

ABO Blood-Type System

The **AB0 blood-type system** is present in multiple alleles (genetic polymorphism). In multiple alleles, there are 2 alleles of 1 gene within a population. In each individual, these alleles behave dominantly/recessively or co-dominantly. In the AB0 system, the following alleles exist:

- A for antigen A
- B for antigen B
- 0 for no antigen

A and B are co-dominant vis-a-vis each other and dominant vis-a-vis 0. They carry antigens in their glycocalyx. In the recessive allele, 0 is concealed and can only be present in homozygosity. The 0 allele does not carry any antigen in the glycocalyx.

MN Blood-Type System

In co-dominance, both alleles simultaneously appear in the phenotype (at heterozygosity). In pure co-dominant inheritance, one can always directly deduct the genotype from the phenotype: no recessive gene that could hide is present. An example of this is the **MN blood-type system**. There are 2 different alleles of a protein in the glycocalyx of the erythrocytes in the MN system.

The following table summarizes the genotypes and resulting phenotypes of the blood type inheritance in the MN system and the AB0 system. These rules of inheritance can be used for an intermittent paternity test. If the blood-type constellation between father and

child does not fit, paternity can be excluded and further genetic tests are not needed.

	Phenotype	Genotype
AB0 system	A	AA, A0
	B	BB, B0
	AB	AB
	0	00
MN system	M	MM
	N	NN
	MN	MN

Rh System: The Rhesus Factor

The **Rhesus factor** is a protein and is inherited dominantly. Rh-negative persons can produce antibodies against the Rh factor, but only after contact with Rh-positive blood. This leads to problems in pregnancy of an Rh-negative mother with an Rh-positive father. During birth, the Rh-positive blood of the child has contact with the maternal blood.

The mother then produces antibodies against Rh. They are able to pass through the placenta during the next pregnancy and agglutinate the Rh-positive erythrocytes in the fetal organism. The consequence is severe jaundice of the child at birth, with severe cerebral damage.

Heterozygous Father Rhrh	Homozygous Father RhRh
Complications develop in 50% of the offspring.	Complications develop in 100% of the offspring.

Antibody Prophylaxis

After the birth of the first child, the mother is injected with a high dose of Rh-antibodies. They mask the child-Rh-antigens and make for a quick elimination; as a result, no maternal Rh-antibodies are produced.

Genomic Imprinting: Marking According to Paternal Origin

Everything you have learned so far shows that most genes are present twice: 1 of the mother's and 1 of the father's. According to Mendel's rules, dominant alleles determine the phenotype. For some kinds of inheritance, however, it has been observed that it is crucial from which parent the affected allele was inherited.

The activity of 1 of the 2 genes is significantly decreased. This marking of paternal genes is referred to as **genomic imprinting**. The imprinting occurs in the development of the germ cells. In about 20 genes, genomic imprinting can be verified.

Genomic imprinting occurs over again in each generation, when the inherited imprints are deleted.

Deletion in the Proximal Section of the q-Arm of Chromosome 15

If a child inherits a defective chromosome from the father, the child will have **Prader-Willi syndrome** (developmental delays, dwarfism, obesity). If a child inherits the defect chromosome from the mother, the child will develop **Angelman syndrome** (disproportioned skull and the face, uncontrolled laughing attacks).

Exercise: Risk Calculation in Human Genetics

Question: Two brothers suffer from a recessively inherited X-chromosomal disease. How great is the risk for their niece (the daughter of the sister) to be a heterozygous conductor?

Solution: Both brothers must have inherited the mutated allele from their mother. As a healthy conductor (X**x**), the mother gives the allele to her daughter (probability of 50% (p = 1/2)). She then gives the mutated allele (probability is 50%) to her children (her husband is healthy and is, thus, not involved in the calculation). The probability for her niece to be affected is calculated via the product of the individual probabilities, i.e., ½ x ½ = ¼ = 25%

References

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Notes