14.1: Mendelian inheritance

There are four basic types of Mendelian inheritance patterns: autosomal dominant, autosomal recessive, X-linked recessive, and X-linked dominant. Autosomal inheritance patterns suggest that the gene responsible for the phenotype is located on one of the twenty-two pairs of autosomes (non-sex determining chromosomes). This is in contrast to X-linked traits where the gene that encodes for the trait is located on the X chromosome.

Traits can be either dominant or recessive in nature such that in the case of dominant traits conditions manifest in heterozygotes (individuals with just one copy of the mutant allele).

Recessive traits

- Recessive conditions are expressed in individuals who have two copies of the mutant allele. Keep in mind, the two recessive alleles may have two different mutations to produce a recessive individual (heteroallelic).
- When just one copy of the mutant allele is present, an individual is a carrier of the mutation but does not develop the condition.
- Females and males are affected equally by traits transmitted by autosomal recessive inheritance.
- A heterozygous carrier for a recessive mutation has a 50 percent probability of transmitting this mutation to a child (figure 14.1).
- If both partners are heterozygous carriers for the same autosomal recessive disease, the risk for transmission to offspring is as follows:
  - 25 percent of the offspring of the couple will be homozygous (or compound heterozygous) for the disease-causing allele and thus be affected by the disorder.
  - 50 percent of the offspring will be healthy heterozygous carriers just as their parents.
  - 25 percent will be homozygous for the wild-type allele.
When speaking of the children of carrier parents, two-thirds of the healthy siblings of an affected child are heterozygous carriers.

If an individual with an autosomal recessive disorder has children, a disease-causing mutation will be transmitted to all of them (either of the two mutant alleles). The consequences for the child depends on this individual's partner. If the partner is homozygous for the normal allele of the respective gene (as in the majority of cases), all offspring will be nonaffected heterozygous carriers. If the partner, however, is a carrier (the likelihood is approximately 0.5 to 1 percent for the more frequent recessive disorders), statistically, half of the offspring will be affected (homozygous or compound heterozygous), and the other half will be carriers. If both partners should have the same recessive disorder (caused by mutations in the same gene), all offspring will be homozygous/compound heterozygous and affected.

**Dominant traits**

- Dominant conditions are expressed in individuals who have just one copy of the mutant allele.
- Females and males are affected equally by traits transmitted in an autosomal dominant fashion.
- Affected individuals have one normal copy of the gene and one mutant copy of the gene; thus each offspring has a 50 percent chance on inheriting the mutant allele (figure 14.2).
Semidominance or incomplete dominance

For most disorders inherited as dominant traits, homozygosity for a disease-causing mutation results in a much more severe clinical phenotype than heterozygosity. An example is familial hypercholesterolemia, a genetic disorder resulting from mutations of the low-density lipoprotein (LDL) receptor gene. Individuals with a heterozygous loss-of-function mutation show elevated LDL cholesterol levels (greater than 7 to 10 mmol/L) and typically suffer their first myocardial infarction in midlife. Homozygous individuals have a much higher LDL cholesterol level (10 to 30 mmol/L), with the onset of symptoms in early childhood and coronary heart disease as early as school age.

In these examples, the phenotype of heterozygotes (Aa) is somewhere in between the phenotypes of wild-type and mutant homozygotes (AA and aa). The inheritance pattern is called semidominant or incompletely dominant, in contrast to complete dominance that is found in very few conditions, such as Huntington's disease, in which the phenotype of the heterozygous and homozygous mutation carriers is more or less identical. It is worth thinking about reasons why a condition may show complete penetrance. For practical purposes, both types of conditions may be called dominant because the definition rests on the clinical phenotype in the heterozygote, irrespective of what is observed in the homozygote.

Codominance

There are a few cases in which two alleles of the same gene code for proteins with different specific functions, both of which may be found simultaneously in (compound) heterozygous individuals. Such alleles are said to be codominant to each other. The classic example is the ABO blood group system, in which individuals with genotype AB show phenotypic characteristics of allele A as well as allele B, and there is also a null allele that causes complete loss of protein function.
Sex-linked traits

X-linked recessive traits do not typically manifest when there is a normal copy of the gene (e.g., in females). In contrast nearly all X-linked recessive traits are fully evident in males because they only have one copy of the X chromosome, and thus do not have a normal copy of the gene to compensate for the mutant copy. For that same reason, women are rarely affected by X-linked recessive diseases, however, they are affected when they have two copies of the mutant allele.

If a man is affected with an X-linked recessive condition:

- All his daughters will inherit one copy of the mutant allele from him; there is no male-to-male transmission.
- All daughters are obligate heterozygotes and may be either asymptomatic carriers or have variable (less severe) symptoms of the disorder.
- On average, 25 percent of the daughters’ children (50 percent of her sons) will be affected with the disorder of their grandfather, 25 percent of children (50 percent of her daughters) will be heterozygous females, while 50 percent of the children will inherit the normal allele from their mother.
- All sons of an affected male will have inherited the Y chromosome of their father and, therefore, will not be affected and will not transmit the disorder to their children.

X-linked dominant disorders clinically manifest when only one copy of the mutant allele is present. There is no transmission from father to son, but there can be transmission from father to daughter (all daughters of an affected male will be affected since the father has only one X chromosome to transmit). Children of an affected woman have a 50 percent chance of inheriting the X chromosome with the mutant allele. Phenotypic presentation of X-linked traits can be influenced by lyonization or X-inactivation. As one X chromosome is randomly expressed in all female cells, the differential patterns of X-inactivation can alter phenotype in female carriers of X-linked recessive disorders and X-linked dominant disorders.

Calculation of risk

One of the most important considerations of genetic counseling is calculating risk. Mathematics is only the first step; equally important is communicating the probability that the event will occur. There are a number of ways to say that an event will not occur with absolute certainty. Studies have shown that these terms are understood and evaluated differently by different individuals. Another factor that varies between patients is that events are evaluated according to whether the result will be considered positive or negative and by which consequences they will have. For example, the probability that, beginning at age forty-five, mothers have a 5 percent risk of giving birth to a child with a chromosomal disorder is generally considered a high risk. In cancer, on the other hand, a survival chance of 5 percent is considered low.

Hardy-Weinberg equations

The Hardy-Weinberg law rests on the assumption that there are two different alleles at a certain locus; these alleles are named "\(p\)" and "\(q\)" (i.e., a normal allele [traditionally \(p\)] and a variant allele [traditionally \(q\)]). Since there are only these two alleles, \(p + q = 1\).
In humans, if the respective gene occurs in two copies on only one autosome, the frequency of the three possible genotypes is calculated from the binominal distribution, which is often represented as:

\[ p^2 + 2pq + q^2 = 1 \]

\( p \) is the frequency of the ‘A’ allele

\( q \) is the frequency of the ‘a’ allele

\( p^2 \) = the frequency of the AA genotype

\( q^2 \) = the frequency of the aa genotype

\( 2pq \) = the frequency of the Aa genotype

The Hardy-Weinberg law only applies to an “ideal population” that meets the following criteria:

- Mating within the population occurs randomly, with equal probability and equal success for the various genotypes.
- The population is large enough to prevent random events (gene drift) from affecting the allele frequency.
- There is no selection advantage or disadvantage for carriers of certain genotypes.
- There are no new mutations.
- There are no migration events that might alter the allele frequency.

The one factor that has practical implications among this group of criteria is random mating, since the Hardy-Weinberg law cannot be applied if there is frequent intermarriage. In such cases, rare recessive disorders occur with much greater frequency than would be expected from the frequency of heterozygosity. The other criteria are more relevant to whether or not the allele or genotype frequencies remain constant or whether the incidence of a disorder changes.

Example

Cystic fibrosis is a recessive condition that affects 1/2,500 births in the Caucasian population:

Frequency of the recessive allele:

\[ q^2 = 1/2,500 = 0.0004 \]

\[ q = 0.02 \]

Frequency of the dominant allele:

\[ 1 - 0.02 = 0.98 = p \]

References and resources

Text


**Figures**


Grey, Kindred, Figure 14.2 Allelic distributions in dominant traits. 2021. [https://archive.org/details/14.2_20210926, CC BY 4.0](https://archive.org/details/14.2_20210926).

**Additional resources**

- Hardy-Weinberg problems: [https://www.k-state.edu/parasitology.../hardwein.html](https://www.k-state.edu/parasitology.../hardwein.html)