

Heredity and Genetics

DNA and Chromosomes

DNA is molecularly arranged as two helices of sugar and phosphate connected by pairs of nitrogenous bases: adenine (A) and thymine (T) always pair together as does guanine (G) and cytosine (C). The double helix of the DNA molecule allows for its exact replication. The specific sequence of base pairs also allows for the transcription to RNA and subsequent translation into protein. The human genome is the totality of the sequence of base pairs in the human species. At cell division, the thread-like DNA in the nucleus, called chromatin, condenses into structures called chromosomes, now visible under a light microscope. Humans have 23 pairs of chromosomes (total=46), one pair of sex chromosomes (XX or XY) and 22 pairs of autosomes. The two chromosomes of a pair are called homologous chromosomes. The arrangement of all the pairs of homologous chromosomes is called a karyotype.

A sequence of base pairs on the DNA that codes for a particular polypeptide or protein is called a gene. The gene is the unit of inheritance. Each gene has a specific location, or locus, on a particular pair of chromosomes. The pairs of chromosomes are homologous meaning that they have the same sequence of genes at the many loci along their length. This is not to say they are identical in their sequence of base pairs, only that they both carry the same genes that code for a particular kind of protein. A fruit fly, for example may have a gene that codes for the protein that imparts red eye color on one of its homologous chromosomes and a gene for white eye color on the other of the pair. Individuals with identical genes at a locus are referred to as homozygous for that gene and if the genes are different, the individual is referred to as heterozygous for the gene. The different genes that are possible at a locus are called alleles. A population of fruit flies may have many alleles for eye color (red, white, purple, green, orange) but of course an individual may only have a maximum of two different alleles at a particular locus. The genetic make-up (the DNA) of an individual is his or her genotype; the trait resulting from that genotype, i.e., what is actually observed, is the phenotype.

Often, if there are different alleles for a particular trait, one gene will mask the expression of the other. This gene is called the dominant gene and the masked, or unexpressed gene is called the recessive gene. Thus, if a fruit fly has the gene for red eyes on one homologous chromosome and the gene for white eyes on another, only the gene for red eyes will be expressed because it is dominant. At meiosis the number of chromosomes is reduced by half, so that only one or the other of the alleles will be found in a particular egg or sperm. We can determine the different possible combinations of gametes with different alleles by drawing a Punnett Square.

For example, the presence of dimples in humans is caused by a dominant gene. We normally represent dominant genes with capital letters, so **D** will represent the gene for dimples and **d** will represent the recessive gene for the absence of dimples. Suppose a woman who is homozygous dominant for dimples (DD) has children by a man who is homozygous recessive with no dimples (dd). When her homologous chromosomes separate during meiosis, what genes will her eggs carry? – Only the gene for dimples (D). When the man's homologous chromosomes separate during spermatogenesis, he too carries only one kind of gene (d) for the absence of dimples.

We can arrange the possible combinations of gametes as follows:

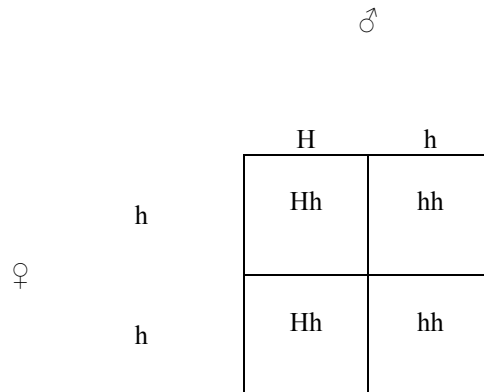
		♂	
		d	d
♀	D	Dd	Dd
	D	Dd	Dd

Notice that there is only one possible combination of alleles when the 2n or diploid number of chromosomes is restored at fertilization - Dd. All of the children will be heterozygous for this trait and all will be dimpled because D is dominant over d. In the next case, let's consider crossing two individuals who are heterozygous. These individuals are able to produce two kinds of gametes - D or d.

		♂	
		D	d
♀	D	DD	Dd
	d	Dd	dd

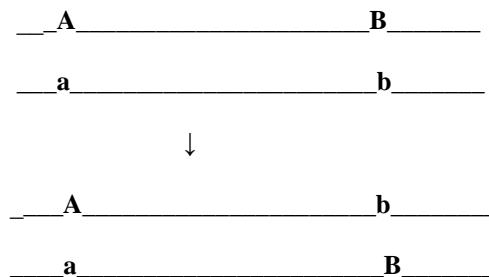
We now have three different genotypes (DD, Dd, and dd) in a ratio of 1:2:1. We only have two phenotypes (dimpled and not dimpled) in a ratio of 3:1.

Huntington's chorea is a disease caused by a dominant gene (H). The normal gene is recessive (h).



You can see that the odds of producing a child that will acquire Huntington's is 1:1 or 50/50. Most genetic disorders are caused by recessive genes. Some recessive disorders are cystic fibrosis, galactosemia, PKU, sickle-cell anemia and Tay-Sachs disease. People who carry this recessive gene but do not exhibit the disorder themselves are termed carriers. A pedigree is a family tree or chart that shows genetic relationships between related individuals.

Remember that during the first meiotic division each chromosome, along with its identical sister chromatid, came to lie next to its homologous chromosome and its sister chromatid. At this point, pieces of chromosome may exchange with its homologue in a process called crossing over. This produces a recombination of genes.



Some traits exhibit incomplete dominance, i.e., the heterozygous individual is a phenotypic mix of the homozygous recessive and the homozygous dominant. The sickle-cell gene is an example of this. Sickle-cell anemia is caused a recessive gene (s) that in the homozygous condition (ss) causes a sickling of red blood cells due to a defect in the β chain of the globin. The normal condition is SS. Heterozygous individuals (Ss) do not show symptoms of the anemia but show an immunity to malaria. People homozygous for the normal gene show no such immunity.

Other genes are codominant, and when both are present, both are expressed. The ABO blood groups are an example of this. The genes for A and B are codominant while the gene for O is recessive. A cross between a person who is homozygous for type A and a person homozygous for type B will produce children only with type AB. Only those homozygous for the recessive gene will be type O.

Gender Determination

The 23rd pair of human chromosomes are the sex chromosomes called the X and Y chromosomes. Males generally have one X chromosome (from their mothers) and one Y chromosome (from their fathers). Females generally have two X chromosomes, one from each parent. On the Y chromosome is (usually) found the SRY gene (Sex-determining Region of the Y chromosome). The SRY gene changes the shape of the DNA and allows for the expression of genes that determine male characteristics. If the SRY gene is somehow inserted on the X chromosome, a person may be genotypically XX but phenotypically male. A mutation of the SRY gene may result in a phenotypic female who is XY.

Some genes are carried on the X chromosome with no corresponding locus on the Y chromosome. These genes are called sex-linked. If a recessive gene is the cause of a genetic disorder, a woman must be homozygous for the disorder to be expressed. A man, on the other hand, will manifest the disorder if a single copy of the recessive gene is present on the X chromosome. Consider the case of hemophilia A:

		♂							
		XH	Y						
	♀	<table border="1" style="border-collapse: collapse; width: 100%; text-align: center;"> <tr> <td style="padding: 5px;">XH</td> <td style="padding: 5px;">XX HH</td> <td style="padding: 5px;">XY H-</td> </tr> <tr> <td style="padding: 5px;">Xh</td> <td style="padding: 5px;">XX Hh</td> <td style="padding: 5px;">XY h-</td> </tr> </table>	XH	XX HH	XY H-	Xh	XX Hh	XY h-	
XH	XX HH	XY H-							
Xh	XX Hh	XY h-							

Red-green colorblindness is another example of a sex-linked gene.

Chromosomal Abnormalities

A chromosomal translocation occurs when a piece of one chromosome breaks off and reattaches to a nonhomologous chromosome. The Philadelphia chromosome (named after the city in which it was discovered) is associated with a kind of chronic leukemia in which a piece of chromosome 22 attaches to a piece of chromosome 9.

Sometimes deletions occur. This is a loss of a chromosome segment. *Cri-du-chat* syndrome is caused by a deletion in chromosome 5 and results in mental retardation and a misshapen larynx.

Down syndrome is caused by an abnormal number of chromosome 21. Instead of the usual two homologous chromosomes there is a third copy. Trisomy 21, as it is called, usually results in mental impairment and may result in heart and skeletal defects and poor motor skills.

There also may be changes in the number of sex chromosomes. Turner syndrome results from the inheritance of one X chromosome with no corresponding X or Y chromosome and is designated as XO. Most XO zygotes abort spontaneously. Survivors are female in appearance but short, infertile and with no secondary sex characteristics. Klinefelter syndrome (XXY) results in males who are tall but usually sterile with no secondary sex characteristics and sometimes mildly impaired mentally. People with XYY condition are usually tall, occasionally mildly retarded but normally male.

Fragile X Chromosome is a cause of mental retardation and autism. In a gene called FMR1 there may be an excessive repetition of the trinucleotide CCG. If this occurs over 200 times, the gene (which is important in neural development) is turned off, i.e. is not expressed.

Genetic Counseling, Genetic Screening, Fetal Testing

Newborns are routinely tested for a number of genetic disorders at birth. One common test is for phenylketonuria. This disorder results in tissue cells unable to utilize the amino acid, phenylalanine. If phenylalanine, present in virtually all protein is not broken down, it accumulates and causes brain damage and mental retardation.

Knowing the parents' pedigree or genetic history enable geneticists to calculate the probability of a child being born with a particular disorder. For example, if a woman is known to be heterozygous for red/green colorblindness, the chances of having a son with this disorder is 50%. Some disorders are not carried as defective genes. Down syndrome, for example, increases with the age of the mother. A woman of 40 has a far greater chance of bearing a Down Syndrome baby than a woman of 35.

Amniocentesis is a common way of fetal testing for genetic disorders. A small amount of amniotic fluid containing fetal cells is drawn off during the 14th week of pregnancy and cultured. DNA probes and karyotypes can then determine if disorders are present. At the 10th week of pregnancy, chorionic villi sampling may be performed but with a little more risk to the fetus. (There is some risk in both procedures.) In this procedure, a small amount of chorionic villus is siphoned off and karyotyping can be done almost immediately since no tissue culture is required.

Gene therapy is a area of intense research. The goal is to replace a defective gene with a normal gene, perhaps using a retrovirus as a vector. Only a few individuals with "bubble-boy" disease, an immune disorder, have been actually cured using gene therapy. A few other disorders, such as cystic fibrosis, have had mixed results.