

In this section we will learn about different types of genetic abnormalities using a specific disorder as an example for each type. Some types involve one gene and one mutant allele that is recessive (sickle cell anemia) or dominant (Huntington disease), others involve one gene but many different mutant alleles (cystic fibrosis), while still others involve multiple genes and multiple mutations (cancer).

Diseases Caused by Single Mutations with Recessive Expression

Sickle Cell Disease

Red Blood Cells Carry Oxygen

As we said earlier, DNA mutations can lead to altered proteins that may or may not

Please note: definitions of terms that are in boldface in the text as well as other terms can be found in the Glossary.

work correctly for the benefit of the cell and organism. As modern molecular techniques now make detecting these mutations relatively easy, more genes are being detected that are associated with particular disorders. For example, you may recall that hemoglobin is a protein

found in red blood cells that transports oxygen from your lungs to the rest of your body. As red blood cells pass through capillaries in the lungs, oxygen passes from the airways into the capillaries, then into the red blood cells. Bound to the hemoglobin, this oxygen is delivered by the blood supply to various tissues. The alleles of the normal gene for hemoglobin are designated HbA and thus a normal gene is designated Hb AA (or HbA/HbA).

Sickle Cell Mutation Can Disturb Oxygen-Carrying Capacity

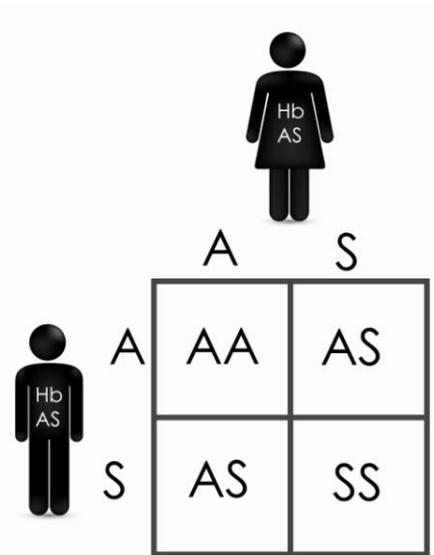
With a certain single subunit change or mutation, the normal allele is changed to a different allele called HbS. This allele is recessive. Thus, for carriers with only one allele, the gene is designated HbAS. As shown in Session 1 (see Genetics 101, "Practical Implications of Genetic Variation: The Story of Blood Types"), this means that the full characteristic or disease associated with the mutation occurs only when both alleles are affected, that is, when the gene is said to be homozygous for the mutation (designated as HbSS). (Among those with the HbAS gene, life expectancy is normal and they are not anemic, but some symptoms of the disease may occasionally occur if the person is unable to breath in enough oxygen, as happens with some lung diseases.)

Hemoglobin molecules produced by the HbS allele tend to stick to one another, producing long, rod-shaped structures that cause the red blood cells to assume a stiff,

elongated shape that looks like a harvesting sickle. These “sickled” cells tend to get trapped in the tiniest blood vessels or capillaries. As a result, the tissues supplied by those capillaries become starved of oxygen and the tissue dies. In carriers, the presence of one HbA allele and its normal hemoglobin molecule offsets the effect of the more recessive HbS allele and sickle cell disease does not occur. Clinical manifestations of those with sickle cell disease (that is, those with HbSS) include shortened life span, severe anemia, impaired growth and development, and unpredictable episodes of severe pain involving joints, abdomen, or chest during sudden occlusion of capillaries in those areas.

Sickle Cell Carrier versus Sickle Cell Disease

Persons homozygous for the HbS allele will have signs and symptoms of sickle cell disease early in life so testing for the mutation will not be necessary. While those homozygous for the normal HbA allele (HbAA) will not have the disease, people who are heterozygous also will not have symptoms of the disease, but are carriers of the HbS allele and could pass it on to one or more offspring. As seen in the Punnett Square constructed in the figure to the right, if two heterozygous individuals have a child, there is a 1 in 4 (25%) chance that the child will receive HbS alleles from both parents and as a result will develop sickle cell disease. If one parent is homozygous for the normal allele while the other is heterozygous, having a child runs a 25% chance that the child will carry sickle cell disease. However, as mentioned above, such a child would not have sickle cell disease.



Other Consequences of Sickle Cell Mutation

While genetic testing can be particularly helpful to determine the likelihood of parents passing on the sickle cell trait or disease to their children, genetic testing is also helpful to determine when genetic screening should be performed in a given population. For example, some ethnic and geographical populations have a very low prevalence of the disease while others, particularly those in Africa and those living around the Mediterranean Sea, have a much higher prevalence. Interestingly, malaria is also often prevalent in the latter populations and there is some evidence that heterozygous carriers of the sickle cell allele (HbAS) are partially protected against malaria. Since the abnormal hemoglobin in sickled cells carries oxygen less efficiently, parasites that infect red blood cells that carry the sickle cell trait seem to survive and replicate less well in

such oxygen-depleted conditions. Homozygotes with the sickle cell disease, however, do not benefit because of the severity of sickle cell disease itself outweighs any protection against malaria. As a consequence, testing citizens of these areas may be helpful in reducing the prevalence of those with the disease. In some countries, such as Cyprus, the prevalence of disease has become such a burden on the cost of health care that young people who carry the trait are discouraged from marrying someone with the trait in order to reduce the prevalence of disease.

Cystic Fibrosis

Normal Function of the Cystic Fibrosis Gene

Cystic fibrosis (CF) is also a genetic disorder that is the result of a mutation in a single gene. In this case, the protein produced by the gene transports salt into and out of cells. If a mutation in the gene results in an abnormally functioning protein, this transport may be disrupted, in which case thick mucous can accumulate outside the cells. In some organs, this abnormality has no impact on function. In the lungs, however, the thick mucous causes difficulty in breathing and provides an environment in which bacteria can grow, leading to pneumonia. In the digestive system, the mucous prevents the secretion of digestive enzymes, leading to digestive problems.

Comparisons with the Sickle Cell Mutation

Unlike the case in sickle cell disease, where the same mutation is present in nearly



A typical human blood cell (left) contrasted with a sickle shaped cell (right).

everyone with the disorder, different mutations of the salt transporter gene can lead to cystic fibrosis. Currently, just over 1400 different mutations have been identified in the salt transporter gene and the severity of the disease varies depending on the mutation involved. However, over 70% of individuals diagnosed with cystic fibrosis have one particular mutation. Because the frequency of the other mutations is so rare, they are not routinely tested. Like the sickle cell mutation, all of these mutations of the salt transporter gene result in recessive alleles. So for an

individual to develop CF, both alleles of the salt transporter gene must be mutated. Also like the sickle cell mutation, the prevalence of the mutation varies among different ethnic groups and nationalities. For example, in the United States, one in 25 (4%) Caucasians of northern European descent (EuroAmericans) carry the mutation. By

contrast, the prevalence among African Americans is less than half that figure (1.5%) and less than one third of the rate found in Asian Americans.

Uncertainties with CF Testing

Unlike the test for sickle cell mutation, a negative test does not mean that an individual is definitely not a carrier because only the most prevalent mutation of CF is routinely tested for. Those who test negative may in fact be heterozygous for another mutated allele not tested for. For example, following testing, the carrier rates of cystic fibrosis for African Americans drops by one third, from 1.5% to 0.5%, but still does not reach zero. As in the case of the sickle cell mutation, such testing might be helpful in identifying higher risk groups. However, it also may miss carriers of rarer CF mutations and thus not give the full picture of carrier rates among different ethnic groups.

Disease Caused by a Single Autosomal Dominant Gene: Huntington Disease

Huntington Disease

The mutated allele that results in Huntington disease (HD) is dominant over the normal allele. This means that a person with only one mutated allele is not just a carrier, but will also develop the disease associated with the mutation. However, unlike persons with sickle cell disease or CF, those with Huntington disease typically develop signs and symptoms around the age of 40 or later rather than in infancy or early childhood. Consequently, genetic testing has a very different meaning for those with the HD mutation.

As with sickle cell disease and CF, individuals who appear healthy but who test positive for the HD allele know that they may pass on the mutation to their offspring. However, as carriers of a dominant allele like HD, they also know that they will eventually develop a deadly, progressive disease sometime later in life and that some offspring will receive the allele and develop the disease – doubly devastating news. This means that someone carrying only one allele has a 50% chance of passing on that allele (and therefore the disease) to any child, regardless of the genotype of the other parent.

Thus, for children with a parent with HD, testing for the HD mutation can be a difficult decision. Some children may choose not to be tested and thus not risk having to live with the knowledge that someday HD will develop. Such testing also has implications for marriage since having the HD mutation carries distinct risks for children to develop HD while not having the mutation carries no risk of future offspring.

Genetically Inherited Increased Risk of Cancer

Genetic Testing for Disorders Involving Single versus Multiple Genes

Although the majority of genetic tests currently available are for single gene disorders like sickle cell disease, cystic fibrosis, and Huntington disease, the majority of disorders associated with genetic changes are not the result of a mutation in a single gene. Multiple genes may be involved and/or genes may interact with the environment to produce a particular type of disorder, such as cancer, diabetes, heart disease, Alzheimer's disease, and others. While genetic testing for these disorders is much more complex and may not provide the precise answers obtained from testing for a single gene disorder, such testing may become more helpful in the future as our understanding of such complex interactions between genes and the environment increases.

BRCA1 Gene and Breast Cancer

Let's use cancer as an example. The development of cancer is a complex process, but the first step is usually a mutation in one of only a few important genes that control normal cell replication. An example of such a gene is the BRCA1 gene. This gene produces a protein that is involved in the regulation of cell division, particularly in certain cells in the breast, by repairing damaged DNA and helping cell division to occur in an orderly fashion. Cancer develops when cells begin dividing uncontrollably. Certain mutations of the BRCA1 gene result in a non-functional protein that fails to repair damaged DNA, resulting in a greater tendency for cells to replicate uncontrollably and a much higher risk of breast cancer. In other words, if a mutation of the gene results in the loss of the ability to stop cell replication, uncontrolled growth may result in cancer development.

Predicting Breast Cancer by Genetic Testing

These genes can develop mutations that markedly increase the risk of breast and ovarian cancer, even if only one allele is affected. The increased cancer risk associated with the inherited, mutated gene may be due to the mutation of the other BRCA1 gene but could also be due to the interaction of the inherited mutated protein with other proteins involved in cell replication. In either case, a woman who inherits a mutation of one of her BRCA1 gene alleles has a very high lifetime risk of developing breast cancer or ovarian cancer. Estimates of risk for breast cancer before the age of 70 vary from about 40% to 70% or greater (the risk of ovarian cancer may be as high as 40%). In addition, such cancers are also more likely to occur at an earlier age than those not linked to a mutation of BRCA 1.

Thus, women with breast cancer that develop at a very early age, or those with a first degree relative who develop breast cancer at a very early age, are eligible for genetic testing. If they test positive for a BRCA1 mutation, they may wish to consider preventative therapy to prevent cancer from recurring. In addition, daughters of such patients may wish to be tested to know whether they have inherited increased susceptibility to develop breast or ovarian cancer.

Diseases Involving Mutations of DNA Located Outside of the Nucleus

As mentioned earlier (in Genetics 101, *A Sidebar...*) there is a small amount of additional genetic material containing DNA outside of the nucleus of cells but within the energy-producing organelle called the mitochondrion. This genetic material is passed on only through the mother's genetic line because the egg carries nearly all of the mitochondrial DNA in its cytoplasm. Genetic testing on this type of DNA has been used to confirm the identity of deceased persons by comparing their DNA with that of a suspected female descendent. An increasing number of distinct health disorders have been associated with mutations of this genetic material and genetic testing for determining the susceptibility of the descendants of affected individuals may be possible. (For more information, see <http://www.ncbi.nlm.nih.gov/books/NBK1224/>.)

Testing Human Embryos for Genetic Mutations

Sometimes, a couple asks to have genetic testing conducted on embryos produced for them by **in vitro fertilization**. This is called **pre-implantation genetic diagnosis** and is performed by carefully removing one of the zygote's cells at the 8-cell stage. The cell is then examined for genetic abnormalities. The remaining 7-celled zygote is allowed to continue to divide and can mature into what appears to be a normal infant at birth. While such zygotes appear to develop normally thereafter, this area has not been well studied. This procedure also has raised ethical issues since the cell that was removed for testing was possibly still totipotent and thus capable of forming an identical infant to the one produced by the remaining 7-cell zygote (see also the section Embryonic Development and Genetic Engineering, Conception and Development of the Embryo).