



## Genes and Cancer

Advances in science have improved our knowledge of the inner workings of cells, the basic building blocks of the body. All living things are made of cells. Complex animals such as humans have trillions of cells. Cells work together to form organs, such as the heart, liver, and skin. Human bodies have several organ systems.

Cancer begins when genes in a cell become abnormal and the cell starts to grow and divide out of control.

### What are genes?

Genes are pieces of DNA (deoxyribonucleic acid) inside each cell that tell the cell what to do and when to grow and divide. Each gene is made up of a specific DNA sequence that contains the code (the instructions) to make a certain protein, each of which has a specific job or function in the body. Each human cell has about 25,000 genes.

Most genes are contained in *chromosomes*. A chromosome is a long strand of DNA wrapped around a special protein called histone. Most chromosomes contain many different genes. Most human cells contain 23 pairs of chromosomes – one pair of sex chromosomes (either XX in females or XY in males) plus 22 pairs of non-sex chromosomes called autosomes. Sperm and egg cells only contain half as many chromosomes (23). Chromosomes are passed from parents to their children through sperm and egg cells. One chromosome of each pair is inherited from the mother, and the other comes from the father. This is why children look like their parents, and why they may have a tendency to develop certain diseases that run in their families.

A cell uses its genes selectively; that is, it can turn on (or activate) the genes it needs at the right moment and turn off other genes that it doesn't need. All the cells in the body (except egg and sperm) contain the same genes. Turning on some genes and turning off others is how a cell becomes specialized. That is how a cell becomes a muscle cell and not a bone cell, for example. Some genes stay active all the time to make proteins needed for basic cell functions. Others shut down when their job is finished and start again later if needed.

### Dominant vs. recessive genes

We have 2 versions (copies) of most genes – one from each parent. For some versions of a gene, only one copy is needed to see a certain quality or disease (in genetics this is called a trait). These genes are called *dominant*. If both copies have to be the same to see that trait, it is called *recessive*. For example, the gene for brown eyes is dominant while the gene for blue eyes is recessive, so if you get one copy of the brown eye gene from one parent and a copy of the blue eye gene from the

other, you will have brown eyes. You will only get blue eyes if you get 2 copies of the blue eye gene (one from each parent). This classification applies to gene mutations as well. If you only need to inherit one copy of a gene mutation to get a disease or syndrome, it is called dominant. If you need 2, it is called recessive. (Gene mutations are discussed in the next section.)

### **X-linked genes**

Things are a little different in terms of genes on the X chromosome. Normally, we each have 2 sex chromosomes. Women have two X chromosomes, while males have one X chromosome and one Y chromosome. Since the Y chromosome contains different genes than the X chromosome, males have only one copy of the genes on the X chromosome. Some diseases/conditions are caused by genes on the X chromosome. For some of these, like color blindness, a female has to have 2 copies of the gene (one on each X chromosome) to get the condition. For a male though, he only has to have the gene on his one X chromosome. Diseases and conditions like this are called *X-linked*. X-linked conditions are more common in males.

## **Changes in genes**

### **Gene mutations**

Mutations are abnormal changes in the DNA of a gene. The building blocks of DNA are called bases. The sequence of the bases determines the gene and its function. Mutations involve changes in the arrangement of the bases that make up a gene. Even a change in just one base among the thousands of bases that make up a gene can have a major effect.

A gene mutation can affect the cell in many ways. Some mutations stop a protein from being made at all. Others may change the protein that is made so that it no longer works the way it should or it may not even work at all. Some mutations may cause a gene to be turned on, and make more of the protein than usual. Some mutations don't have a noticeable effect, but others may lead to a disease. For example, a certain mutation in the gene for hemoglobin causes the disease sickle cell anemia.

Cells become cancer cells largely because of mutations in their genes. Often many mutations are needed before a cell becomes a cancer cell. The mutations may affect different genes that control cell growth and division. Some of these genes are called tumor suppressor genes. Mutations may also cause some normal genes to become cancer-causing genes known as oncogenes (oncogenes and tumor suppressor genes are discussed in more detail later).

We have 2 copies of most genes, one from each chromosome in a pair. In order for a gene to stop working completely and potentially lead to cancer, both copies have to be “knocked out” with mutations. That means for most genes, it takes 2 mutations to make that gene stop working completely.

### **Types of mutations**

There are 2 major types of gene mutations, inherited and acquired:

- An inherited gene mutation is present in the egg or sperm that formed the child. After the egg is fertilized by the sperm, it created one cell called a zygote that then divided to create a fetus (which became a baby). Since all the cells in the body came from this first cell, this kind of mutation is in every cell in the body (including some eggs or sperm) and so can be passed on to

the next generation. This type of mutation is also called *germline* (because the cells that develop into eggs and sperm are called germ cells) or *hereditary*. Inherited mutations are thought to be a direct cause of only a small fraction of cancers.

- An acquired mutation is not present in the zygote, but is acquired some time later in life. It occurs in one cell, and then is passed on to any new cells that are the offspring of that cell. This kind of mutation is not present in the egg or sperm that formed the fetus, so it cannot be passed on to the next generation. Acquired mutations are much more common than inherited mutations. Most cancers are caused by acquired mutations. This type of mutation is also called *sporadic*, or *somatic*.

## Mutations and cancer

Experts agree that it takes more than one mutation in a cell for cancer to occur. When someone has inherited an abnormal copy of a gene, though, their cells already start out with one mutation. This makes it all the easier (and quicker) for enough mutations to build up for a cell to become cancer. That is why cancers that are inherited tend to occur earlier in life than cancers of the same type that are not inherited.

Even if you were born with healthy genes, some of them can become changed (mutated) over the course of your life. These acquired mutations cause most cases of cancer. Some acquired mutations can be caused by things that we are exposed to in our environment, including cigarette smoke, radiation, hormones, and diet. Other mutations have no clear cause, and seem to occur randomly as the cells divide. In order for a cell to divide to make 2 new cells, it has to copy all of its DNA. With so much DNA, sometimes mistakes are made in the new copy (like typos). This leads to DNA changes (mutations). Every time a cell divides, it is another opportunity for mutations to occur. The numbers of gene mutations build up over time, which is why we have a higher risk of cancer as we get older.

It is important to realize that gene mutations happen in our cells all the time. Usually, the cell detects the change and repairs it. If it can't be repaired, the cell will get a signal telling it to die in a process called *apoptosis*. But if the cell doesn't die and the mutation is not repaired, it may lead to a person developing cancer. This is more likely if the mutation affects a gene involved with cell division or a gene that normally causes a defective cell to die.

Some people have a high risk of developing cancer because they have inherited mutations in certain genes. To learn more about this, see our document *Family Cancer Syndromes*.

## Penetrance

For dominant genes and mutations, the term penetrance is used to indicate the proportion of those carrying a mutation who will have the trait, syndrome, or disease. If all of the people who inherit the mutation have the disease, it is called *complete penetrance*. If not all of the people who have the mutation get the disease, it is called *incomplete penetrance*. In general, inherited mutations leading to cancer have incomplete penetrance, meaning not everyone with the mutation will get cancer. That is in part because although the person has a mutation in one copy of the gene, he or she needs to acquire at least one more mutation for the gene to stop working completely and cancer to occur. Since not everyone gets the second mutation, not everyone gets cancer. Incomplete penetrance can also be because even if the mutation makes it so that a gene doesn't function, other factors may be needed for the cancer to start.

## High vs. low penetrance

Gene mutations can cause large changes in the function of a gene. They may even cause that copy of the gene to stop working altogether. When an inherited mutation has a large enough effect on the function of a gene to cause a disease or noticeable problem in most of the people who have it, that mutation is called “high penetrance.”

High-penetrance mutations in cancer susceptibility genes can lead to many people in a family getting certain kinds of cancers – a family cancer syndrome. These are thought to cause only a small fraction of cancers that run in a family. For example, only about 1/5 of the breast cancer that runs in families is thought to be caused by high-penetrance mutations in genes like *BRCA1* and *BRCA2*.

Some inherited mutations, though, don’t seem to affect gene function very much and don’t often cause obvious problems. These mutations are called “low-penetrance.” Low-penetrance mutations can affect cancer risk through subtle effects on things like hormone levels, metabolism, or other things that interact with risk factors for cancer. Low-penetrance mutations, together with gene variants (discussed below) are thought to be responsible for most of the cancer risk that runs in families.

## Gene variants

People can also have different versions of genes that are not mutations. Common differences in genes are called *variants*. These versions are inherited and are present in every cell of the body. The most common type of gene variant involves a change in only one base (nucleotide) of a gene. These are called single nucleotide polymorphisms (SNPs, pronounced “snips”). There are estimated to be millions of SNPs in each person’s DNA.

Other types of variants are less common. Many genes contain sequences of bases that are repeated over and over. A common type of variant involves a change in the number of these repeats.

Some variants have no apparent effect on the function of the gene. Others tend to influence the function of genes in a subtle way, such as making them slightly more or less active. These changes don’t cause cancer directly, but can make someone more likely to get cancer by affecting things like hormone levels and metabolism. For example, some gene variants affect levels of estrogen and progesterone, which can affect the risk of breast and endometrial cancers. Others can affect the breakdown of toxins in cigarette smoke, making a person more likely to get lung and other cancers.

Gene variants can also play a role in diseases that impact cancer risk – like diabetes and obesity.

Variants and low-penetrance mutations can be similar. The main difference between the two is how common they are. Mutations are rare, while gene variants are more common.

Still, since these variants are common and someone can have many of them, their effect can add up. Studies have shown that these variants can influence cancer risk and, together with low penetrance mutations, they may account for a large part of the cancer risk that runs in families.

## Other ways cells change genes and gene activity

Although all of the cells of your body contain the same genes (and DNA), different genes are active in some cells than in others. Even within a certain cell, some genes are active at some times and inactive at others. Turning on and off of genes in this case isn't based on changes in the DNA sequence (like mutations), but by other means called *epigenetic* changes.

**DNA methylation:** In this type of epigenetic change, a molecule called a methyl group is attached to certain nucleotides. This changes the structure of the DNA so that the gene can't start the process of making the protein for which it codes (this process is called transcription). This basically turns off the gene. In some people with a mutation in one copy of a cancer susceptibility gene, the other copy of the gene becomes inactive not by mutation, but by methylation.

**Histone modification:** Chromosomes are made up of DNA wrapped around proteins called histones. Histone proteins can be changed by adding (or subtracting) something called an acetyl group. Adding acetyl groups (acetylation) can activate (turn on) that part of the chromosome, while taking them away (deacetylation) can deactivate it (turn it off). Methylation is also used to activate and deactivate parts of chromosomes. Histone proteins can also be changed by adding or subtracting methyl groups (methylation and demethylation). Although abnormal histone modification isn't known to cause cancer, drugs that alter histone modifications can help in the treatment of cancer by turning on genes that help control cell growth and division.

**RNA interference:** RNA (ribonucleic acid) is important inside cells as the middle step that allows genes to code for proteins. But some small forms of RNA can interfere with gene expression by attaching to other pieces of RNA, or even affecting histones or DNA itself. Drugs are being developed that affect abnormal genes in cancer cells through RNA interference.

## Oncogenes and tumor suppressor genes

Two of the main types of genes that play a role in cancer are oncogenes and tumor suppressor genes.

### Oncogenes

Proto-oncogenes are genes that normally help cells grow. When a proto-oncogene mutates (changes) or there are too many copies of it, it becomes a "bad" gene that can become permanently turned on or activated when it is not supposed to be. When this happens, the cell grows out of control, which can lead to cancer. This bad gene is called an oncogene.

It may be helpful to think of a cell as a car. For it to work properly, there need to be ways to control how fast it goes. A proto-oncogene normally functions in a way that is much like a gas pedal. It helps the cell grow and divide. An oncogene could be compared with a gas pedal that is stuck down, which causes the cell to divide out of control.

A few cancer syndromes are caused by inherited mutations of proto-oncogenes that cause the oncogene to be turned on (activated). But most cancer-causing mutations involving oncogenes are acquired, not inherited. They generally activate oncogenes by:

- **Chromosome rearrangements:** Changes in chromosomes that put one gene next to another, which allows one gene to activate the other

- Gene duplication: Having extra copies of a gene, which can lead to it making too much of a certain protein

## Tumor suppressor genes

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly, just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, cell division can get out of control.

An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the *activation* (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are *inactivated* (turned off).

Inherited abnormalities of tumor suppressor genes have been found in some family cancer syndromes. They cause certain types of cancer to run in families. But most tumor suppressor gene mutations are acquired, not inherited.

For example, abnormalities of the *TP53* gene (which codes for the p53 protein) have been found in more than half of human cancers. Acquired mutations of this gene appear in a wide range of cancers.

## How genes can help in the diagnosis and treatment of cancer

We have already talked about ways genes, gene mutations, and gene variations can affect cancer risk and even lead to cancer. In this section, we are going to talk about how finding certain genes or gene mutations can be helpful in diagnosing cancer, monitoring the effects of treatment, learning about prognosis (outlook), and in treating cancer. In each case, only one or two examples are given. To learn about how genes are important to other kinds of cancer, see our document about that kind of cancer.

### Cancer diagnosis and monitoring treatment

Certain mutations are commonly found in the cells of some types of cancers. Finding certain mutations in cells can confirm the diagnosis of that cancer. Testing cells for the mutation can also be used after diagnosis to see how the cancer is responding to treatment.

For example, the leukemia cells of patients with chronic myeloid leukemia (CML) contain a mutated gene called *BCR-ABL*. In order to be diagnosed with CML, this mutation must be present, so testing for this mutation is used to confirm the diagnosis. Very sensitive tests can tell how many copies of this mutation are present in a blood sample (which indicates how many CML cells are present). These tests can find even tiny amounts, representing small numbers of CML cells among millions of normal cells. The number of copies is determined when treatment is started, and then again sometime later to see how well the treatment is working. If treatment has put the leukemia into remission, this test can be used to see if it is coming back and new treatment is needed.

## Genes and cancer prognosis

In some cancers, specific gene changes can be used to predict which patients are likely to have a better or worse outcome. This can help guide the intensity of treatment.

For example, patients with acute myeloid leukemia (AML) whose leukemia cells have a mutation in the *FLT3* gene have a poorer prognosis than patients whose leukemia cells do not contain that mutation. Doctors may recommend more intense treatment, including stem cell transplant for someone whose leukemia cells have this mutation. On the other hand, people whose leukemia cells have mutations in the *NPM1* gene (and no other abnormalities) seem to have a better prognosis than people without this mutation. As a result, doctors may not feel that a stem cell transplant is needed in someone whose leukemia cells only have a *NPM1* mutation.

For some cancers, tests that look at the activity (expression) of many genes at once can be useful in predicting prognosis. These tests, called *gene expression panels*, are performed on samples of the cancer. They are available for a number of cancers, including breast, colon, and prostate cancers. These tests can help predict which patients are more likely to have their cancers come back after treatment. So far, though, only one, the Oncotype Dx<sup>®</sup> breast cancer assay, has been shown to help predict which patients benefit the most from certain treatments.

## Genes and cancer treatment

### Drugs targeting genes or gene mutations

Drugs have been developed that target some of the gene changes in certain cancers. Actually these drugs often target the protein made by the abnormal gene (and not the gene itself).

For example, *HER2/neu* is a proto-oncogene in normal cells that helps them grow. It becomes an oncogene when a cell has too many copies of this gene. When this happens, the cells make too much HER2/neu protein and the cancer is said to be HER2 positive. Patients with breast cancer with cells that are HER2 positive do not respond as well to certain chemotherapy drugs. But newer drugs such as trastuzumab (Herceptin<sup>®</sup>), lapatinib (Tykerb<sup>®</sup>), and several others, have been designed to specifically attack cells that are HER2 positive. These drugs can slow cancer cell growth and improve outcomes in patients with HER2 positive cancers. Breast cancers are now routinely tested to see if they are or the HER2 positive to identify which patients will benefit from these drugs. Other cancers also can be HER2 positive. Anti-HER2 therapy has also helped people with stomach cancer that is HER2-positive.

In chronic myeloid leukemia (CML), the cancer cells have a gene change called *BCR-ABL* that makes a type of protein called a tyrosine kinase. Drugs that target the BCR-ABL protein, such as imatinib (Gleevec<sup>®</sup>), are often very effective against CML. They lead to remission of the leukemia in most patients treated in the early stages of their disease.

Drugs targeting certain mutations are useful in a number of other cancers including acute lymphocytic leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, a certain kind of non-Hodgkin lymphoma, and melanoma.

## Drugs that activate genes

DNA methylation is one way to turn-off genes. Drugs called hypomethylating agents can reverse methylation. This can be helpful in treating some cancers in which some genes are abnormally methylated. For example, in myelodysplastic syndrome, certain genes that are often methylated in the cancer cells when they aren't supposed to be. The hypomethylating agents decitabine (Dacogen<sup>®</sup>) and azacytidine (Vidaza<sup>®</sup>) can decrease this abnormal methylation, which can be useful in treating this disease.

Other drugs that help fight cancer by activating genes are the histone deacetylase inhibitors, such as vorinostat (Zolinza<sup>®</sup>) and romidepsin (Istodax<sup>®</sup>).

## Gene testing to help predict if a drug will work

Some drugs don't help patients if the cancer cells have certain gene mutations. For example, cetuximab (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>®</sup>) are drugs used to treat advanced colorectal cancers. However, these drugs don't help patients with cancers that have mutations in the *KRAS* gene, so doctors check the cancer cells for these mutations before they give either of these drugs.

Some drugs work better in people with certain mutations. For example, the drug erlotinib (Tarceva<sup>®</sup>), which can be used to treat non-small cell lung cancer, works better in patients whose cancer cells have a certain mutation in the *EGFR* gene.

## Future directions

Many researchers are very hopeful about the future of cancer treatments based on the specific gene changes found in cancer cells, and this remains a very active area of research. There are many clinical trials under way today that could lead to better treatments for many types of cancer.

## To learn more

### More information from your American Cancer Society

We have some related information that may also be helpful to you. These materials may be viewed on our website or ordered from our toll-free number, at 1-800-227-2345.

Genetic Testing: What You Need to Know

Family Cancer Syndromes

### National organizations and Web sites\*

Along with the American Cancer Society, other sources of information and support include:

#### **National Cancer Institute**

Toll-free number: 1-800-4-CANCER (1-800-422-6237)

Website: [www.cancer.gov](http://www.cancer.gov)



Provides accurate, up-to-date information on a variety of cancer-related topics such as finding support, financial assistance and other resources; coping with cancer; cancer genetics, etc. (click the "Cancer Topics" tab on the home page). Also has an Online Cancer Genetics Services Directory to identify professionals who provide services related to cancer genetics (cancer risk assessment, genetic counseling, genetic susceptibility testing, and others). The direct link is [www.cancer.gov/search/geneticsservices](http://www.cancer.gov/search/geneticsservices).

### **National Society of Genetic Counselors (NSGC)**

Telephone: 1-312-321-6834

Website: [www.nsgc.org](http://www.nsgc.org)

Offers a "Consumer Information" link with the following:

- "Making Sense of Your Genes" – a 24-page guide to genetic counseling (may be downloaded and printed)
- Directory of genetic counselors – may be searched by your area
- "Five Questions to Ask Before Considering Genetic Testing" (may be downloaded and printed)
- Guide on collecting family history – a helpful tool in determining possible genetic risks
- FAQs on genetic testing and genetic counselors

*\*Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for cancer-related information and support. Call us at **1-800-227-2345** or visit [www.cancer.org](http://www.cancer.org).

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