

TP53 Gene

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Tumor protein p53: The TP53 gene provides instructions for making a protein called tumor protein p53 (or p53).

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1. Normal Function

The *TP53* gene provides instructions for making a protein called tumor protein p53 (or p53). This protein acts as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing (proliferating) too fast or in an uncontrolled way.

The p53 protein is located in the nucleus of cells throughout the body, where it attaches (binds) directly to DNA. When the DNA in a cell becomes damaged by agents such as toxic chemicals, radiation, or ultraviolet (UV) rays from sunlight, this protein plays a critical role in determining whether the DNA will be repaired or the damaged cell will self-destruct (undergo apoptosis). If the DNA can be repaired, p53 activates other genes to fix the damage. If the DNA cannot be repaired, this protein prevents the cell from dividing and signals it to undergo apoptosis. By stopping cells with mutated or damaged DNA from dividing, p53 helps prevent the development of tumors.

Because p53 is essential for regulating DNA repair and cell division, it has been nicknamed the "guardian of the genome."

2. Health Conditions Related to Genetic Changes

2.1. Breast cancer

Inherited changes in the *TP53* gene greatly increase the risk of developing breast cancer, as well as several other forms of cancer, as part of a rare cancer syndrome called Li-Fraumeni syndrome (described below). These mutations are thought to account for only a small fraction of all breast cancer cases.

Noninherited (somatic) mutations in the *TP53* gene are much more common than inherited mutations, occurring in 20 to 40 percent of all breast cancers. These somatic mutations are acquired during a person's lifetime and are present only in cells that become cancerous. The cancers associated with somatic mutations do not occur as part of a cancer syndrome. Most of these mutations change single protein building blocks (amino acids) in the p53 protein, which reduces or eliminates the protein's tumor suppressor function. This altered p53 protein cannot regulate cell proliferation effectively. Specifically, it is unable to trigger apoptosis in cells with mutated or damaged DNA. As a result, DNA damage can accumulate in cells. Such cells may continue to divide in an uncontrolled way, leading to tumor growth.

Compared with breast cancers without *TP53* gene mutations, tumors with these genetic changes tend to have a poorer prognosis: They are more likely to be aggressive, to be resistant to treatment with certain anti-cancer drugs and radiation, and to come back (recur) after treatment.

2.2. Bladder cancer

Somatic *TP53* gene mutations have been found in some cases of bladder cancer. Bladder cancer is a disease in which certain cells in the bladder become abnormal and multiply uncontrollably to form a tumor. Bladder cancer may cause blood in the urine, pain during urination, frequent urination, the feeling of needing to urinate without being able to, or lower back pain.

Bladder cancer is generally divided into two types, non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), based on where in the bladder the tumor is located. About half of NMIBC tumors have *TP53* gene mutations. Most of these mutations change single amino acids in p53. This altered p53 protein cannot regulate cell growth

and division and is unable to trigger apoptosis in cells with mutated or damaged DNA. As a result, DNA damage can accumulate in cells. If such cells continue to divide in an uncontrolled way, they can lead to the formation of bladder cancer.

2.3. Head and neck squamous cell carcinoma

Somatic mutations in the *TP53* gene have been found in nearly half of all head and neck squamous cell carcinomas (HNSCC). This type of cancerous tumor occurs in the moist lining of the mouth, nose, and throat. Most of the *TP53* gene mutations involved in HNSCC change single amino acids in p53; these changes impair the protein's function. Without functioning p53, cell proliferation is not regulated. As a result, cells accumulate DNA damage and continue to divide in an uncontrolled way, leading to tumor growth.

2.4. Li-Fraumeni syndrome

Although somatic mutations in the *TP53* gene are found in many types of cancer, Li-Fraumeni syndrome appears to be the only cancer syndrome associated with inherited mutations in this gene. This condition greatly increases the risk of developing several types of cancer, including breast cancer; bone cancer; and cancers of soft tissues (such as muscle) called soft tissue sarcomas, particularly in children and young adults. At least 140 different mutations in the *TP53* gene have been identified in individuals with Li-Fraumeni syndrome.

Many of the mutations associated with Li-Fraumeni syndrome change single amino acids in the part of the p53 protein that binds to DNA. Other mutations delete small amounts of DNA from the gene. These mutations result in an altered p53 protein that cannot regulate cell proliferation effectively and is unable to trigger apoptosis in cells with mutated or damaged DNA. As a result, DNA damage can accumulate in cells. Such cells may continue to divide in an uncontrolled way, leading to the growth of tumors.

2.5. Lung cancer

Somatic mutations in the *TP53* gene have been found in nearly half of all lung cancers. Lung cancer is a disease in which certain cells in the lungs become abnormal and multiply uncontrollably to form a tumor. Signs and symptoms may not occur in early stages of the disease.

Lung cancer is generally divided into two types, small cell lung cancer and non-small cell lung cancer, based on the size of the affected cells when viewed under a microscope. Small cell lung cancers nearly always have *TP53* gene mutations; however, these mutations may also occur in non-small cell lung cancer. *TP53* gene mutations change single amino acids in p53, which impair the protein's function. Without functioning p53, cell proliferation is not regulated effectively and DNA damage can accumulate in cells. Such cells may continue to divide in an uncontrolled way, leading to tumor growth. Additional genetic, environmental, and lifestyle factors contribute to a person's cancer risk; in lung cancer, the greatest risk factor is being a long-term tobacco smoker.

2.6. Ovarian cancer

Somatic *TP53* gene mutations are common in ovarian cancer, occurring in almost half of ovarian tumors. These mutations result in a p53 protein that is less able to control cell proliferation. Specifically, it is unable to trigger apoptosis in cells with mutated or damaged DNA. As a result, DNA damage can accumulate in cells. Such cells may continue to divide in an uncontrolled way, leading to tumor growth.

2.7. Other cancers

Somatic mutations in the *TP53* gene are the most common genetic changes found in human cancer, occurring in about half of all cancers. In addition to the cancers described above, somatic *TP53* gene mutations have been identified in several types of brain tumor, colorectal cancer, liver cancer, a type of bone cancer called osteosarcoma, a cancer of muscle tissue called rhabdomyosarcoma, and a cancer called adrenocortical carcinoma that affects the outer layer of the adrenal glands (small hormone-producing glands on top of each kidney).

Most *TP53* mutations change single amino acids in the p53 protein, which leads to the production of an altered version of the protein that cannot control cell proliferation and is unable to trigger apoptosis in cells with mutated or damaged DNA. As a result, DNA damage can accumulate in cells. Such cells may continue to divide in an uncontrolled way, leading to tumor growth.

Cholangiocarcinoma

Melanoma

Wilms tumor

3. Other Names for This Gene

- antigen NY-CO-13
- cellular tumor antigen p53
- P53
- P53 tumor suppressor
- P53_HUMAN
- phosphoprotein p53
- transformation-related protein 53
- TRP53
- tumor protein p53 (Li-Fraumeni syndrome)
- tumor suppressor p53

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