CDKN2A Gene

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cyclin dependent kinase inhibitor 2A

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1. Normal Function

The *CDKN2A* gene provides instructions for making several proteins. The most well-studied are the p16(INK4A) and the p14(ARF) proteins. Both function as tumor suppressors, which means they keep cells from growing and dividing too rapidly or in an uncontrolled way. Both proteins are also involved in stopping cell division in older cells (senescence).

The p16(INK4A) protein attaches (binds) to two other proteins called CDK4 and CDK6. These proteins help regulate the cell cycle, which is the cell's way of replicating itself in an organized, step-by-step fashion. CDK4 and CDK6 normally stimulate the cell to continue through the cycle and divide. However, binding of p16(INK4A) blocks CDK4's or CDK6's ability to stimulate cell cycle progression. In this way, p16(INK4A) controls cell division. Cells begin to produce p16(INK4A) when they are no longer able to undergo cell division.

The p14(ARF) protein protects a different protein called p53 from being broken down. The p53 protein is an important tumor suppressor that is essential for regulating cell division, senescence, and self-destruction (apoptosis). By protecting p53, p14(ARF) also helps prevent tumor formation. The p14(ARF) and p53 proteins are often made in cells that are unable to undergo cell division.

2. Health Conditions Related to Genetic Changes

2.1. Bladder cancer

Bladder cancer

2.2. Head and Neck Squamous Cell Carcinoma

Mutations in the *CDKN2A* gene are found in up to one-quarter of head and neck squamous cell carcinomas (HNSCC). This type of cancerous tumor occurs in the moist lining of the mouth, nose, and throat. *CDKN2A* gene mutations associated with this condition are acquired during a person's lifetime and are found only in tumor cells; these changes are known as somatic mutations. Most of these mutations lead to production of little or no functional p16(INK4A) protein. Without p16(INK4A) to regulate cell growth and division (proliferation), cells can continue to grow and divide without control, which can lead to tumor formation.

A different type of alteration involving the *CDKN2A* gene can result in reduced amounts or an absence of the p16(INK4A) or p14(ARF) protein. This alteration, known as promoter hypermethylation, turns off the production of p16(INK4A) or p14(ARF). Without one of these tumor suppressors, cells can grow and divide unchecked, leading to the development of cancer.

2.3. Lung Cancer

Lung cancer

2.4. Melanoma

Mutations in the *CDKN2A* gene are also associated with melanoma, a type of skin cancer that begins in pigment-producing cells called melanocytes. *CDKN2A* gene mutations are found in up to 40 percent of familial cases of melanoma, in which multiple family members develop the cancer. These mutations, classified as germline mutations, are typically

inherited and are present in essentially all of the body's cells. The *CDKN2A* gene mutations found in melanoma result in a nonfunctional p16(INK4A) protein. In many cases, a second, somatic mutation occurs in the normal copy of the gene in melanocytes. In about half of melanomas, part or all of the *CDKN2A* gene is missing (deleted). In many other cases, the *CDKN2A* gene has a mutation or is turned off (inactive). Somatic mutations in other genes involved in cell growth are also needed for a melanoma to develop. Together, the germline and somatic mutations impair the function of proteins that regulate division and senescence, leading to uncontrolled cell growth and the formation of a melanoma.

Individuals with a *CDKN2A* gene mutation tend to develop melanoma at an earlier age than those without a mutation in the gene. They also tend to develop other cancers during their lifetime, particularly cancers of the pancreas or lung.

2.5. Other Cancers

Germline mutations affecting the *CDKN2A* gene are associated with other cancers, including breast cancer and pancreatic cancer. In some families, *CDKN2A* gene mutations are associated with development of only one type of cancer. In other families, mutations can lead to a cancer predisposition syndrome, which increases the risk of developing multiple types of cancer. *CDKN2A* gene mutations involved in cancer impair production of functional p16(INK4A) or, less commonly, p14(ARF), which can result in uncontrolled cell growth and tumor formation.

Somatic *CDKN2A* gene mutations have been found in some people with brain tumors and in children with a blood cancer called acute lymphoblastic leukemia.

3. Other Names for This Gene

- ARF
- CDK4 inhibitor p16-INK4
- CDK4I
- CDKN2
- cell cycle negative regulator beta
- CMM2
- cyclin-dependent kinase 4 inhibitor A
- cyclin-dependent kinase inhibitor 2A
- cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)
- cyclin-dependent kinase inhibitor 2A isoform p12
- cyclin-dependent kinase inhibitor 2A isoform p14ARF
- cyclin-dependent kinase inhibitor 2A isoform p16gamma
- cyclin-dependent kinase inhibitor 2A isoform p16INK4a
- INK4
- INK4A
- MLM
- MTS-1
- MTS1
- multiple tumor suppressor 1
- P14
- P14ARF
- P16
- P16-INK4A
- P16INK4
- P16INK4A
- P19
- P19ARF
- TP16

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