CDKN1C Gene

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cyclin dependent kinase inhibitor 1C

genes

1. Normal Function

The *CDKN1C* gene provides instructions for making a protein that helps regulate growth. This protein acts as a tumor suppressor, which means that it keeps cells from growing and dividing too fast or in an uncontrolled way. It also is involved in controlling growth before birth, preventing the developing fetus from becoming too large.

People inherit one copy of most genes from their mother and one copy from their father. Both copies are typically active, or "turned on," in cells. However, the activity of the *CDKN1C* gene depends on which parent it was inherited from. In most tissues, the copy of the gene inherited from a person's mother (the maternally inherited copy) has much higher activity than the copy inherited from the father (the paternally inherited copy). This sort of parent-specific difference in gene activation is caused by a phenomenon called genomic imprinting.

CDKN1C is part of a cluster of genes on the short (p) arm of chromosome 11 that undergo genomic imprinting. A nearby region of DNA known as imprinting center 2 (IC2) or KvDMR controls the parent-specific genomic imprinting of *CDKN1C* and several other genes thought to help regulate growth. The IC2 region undergoes a process called methylation, which is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. Methylation, which occurs during the formation of an egg or sperm cell, is a way of marking or "stamping" the parent of origin. The IC2 region is normally methylated only on the maternally inherited copy of chromosome 11.

2. Health Conditions Related to Genetic Changes

2.1. Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is a condition that causes overgrowth and has other signs and symptoms that affect many parts of the body. At least half of all cases of Beckwith-Wiedemann syndrome result from changes in methylation of the IC2 region. Specifically, the maternally inherited copy of the IC2 region has too few methyl groups attached (hypomethylation). This abnormality disrupts the regulation of several genes that are normally

controlled by IC2, including *CDKN1C*. Because this gene normally restrains cell growth and division, a reduction in its activity leads to overgrowth and the other features of Beckwith-Wiedemann syndrome.

In a few cases, Beckwith-Wiedemann syndrome has been caused by deletions of a small amount of DNA from the maternally inherited copy of the IC2 region. Like abnormal methylation, these deletions disrupt the activity of several genes, including *CDKN1C*.

Beckwith-Wiedemann syndrome can also result from mutations within the maternally inherited copy of the *CDKN1C* gene. More than two dozen such mutations have been identified. Some of these genetic changes lead to an abnormally short, nonfunctional version of the CDKN1C protein, while others alter single protein building blocks (amino acids) or delete a small number of amino acids from the protein. All of these mutations are described as "loss-of-function" because they alter the structure of the CDKN1C protein such that it can no longer control growth effectively. The resulting problems with growth regulation lead to overgrowth and the other features of Beckwith-Wiedemann syndrome.

2.2. Intrauterine Growth Restriction, Metaphyseal Dsplasia, Adrenal Hypoplasia Congenita, and Genital Anomalies

Intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies, commonly known by the acronym IMAGe, is a rare syndrome that affects the growth of many parts of the body. The condition is characterized by slow growth before and after birth, skeletal abnormalities, hormonal changes, and genital abnormalities in males. At least six mutations in the *CDKN1C* gene have been found to cause this condition. Because this gene is paternally imprinted, IMAGe syndrome results only when the mutation is present on the maternally inherited copy of the gene.

The *CDKN1C* gene mutations that cause IMAGe syndrome replace single amino acids in a region known as the proliferating cell nuclear antigen (PCNA)-binding domain near the end of the gene. These mutations appear to increase the stability of the CDKN1C protein, preventing it from being broken down normally. These changes increase the amount of the protein that is available to restrain cell growth and division. Because these mutations enhance the protein's usual function, they are described as "gain-of-function." The excess CDKN1C protein leads to IMAGe syndrome by impairing normal growth and development starting before birth.

3. Other Names for This Gene

- BWCR
- CDN1C_HUMAN
- cyclin-dependent kinase inhibitor 1C
- cyclin-dependent kinase inhibitor 1C (p57, Kip2)
- cyclin-dependent kinase inhibitor p57
- KIP2

- p57
- p57KIP2

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