IGF2 gene
insulin like growth factor 2

Normal Function

The IGF2 gene provides instructions for making a protein called insulin-like growth factor 2. This protein plays an essential role in growth and development before birth. Studies suggest that insulin-like growth factor 2 promotes the growth and division (proliferation) of cells in many different tissues. Although the IGF2 gene is highly active during fetal development, it is much less active after birth.

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 IGF2 gene depends on which parent it was inherited from. Only the copy inherited from a person's father (the paternally inherited copy) is active; the copy inherited from the mother (the maternally inherited copy) is not active. This parent-specific difference in gene activation is caused by a phenomenon called genomic imprinting.

IGF2 is part of a cluster of genes on the short (p) arm of chromosome 11 that undergoes genomic imprinting. Another gene in this cluster, H19, is also involved in growth and development. A nearby region of DNA known as imprinting center 1 (IC1) or the H19 differentially methylated region (H19 DMR) controls the parent-specific genomic imprinting of both the IGF2 and H19 genes. The IC1 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 IC1 region is normally methylated only on the paternally inherited copy of chromosome 11.

Health Conditions Related to Genetic Changes

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome, a condition characterized by overgrowth and other signs and symptoms that affect many parts of the body, can result from changes that affect the IC1 region. In some people with this condition, the maternally inherited copy of the IC1 region is methylated along with the paternally inherited copy. Because the IC1 region controls the genomic imprinting of the IGF2 and H19 genes, this abnormality disrupts the regulation of both genes. Specifically, abnormal methylation of the IC1 region leads to increased IGF2 gene activity and a loss of H19 gene activity in many tissues. An increase in IGF2 gene activity, which promotes growth, and a loss of H19 gene activity, which normally restrains growth, together lead to overgrowth in people with Beckwith-Wiedemann syndrome.
In a few cases, Beckwith-Wiedemann syndrome has been caused by deletions of a small amount of DNA from the IC1 region. Like abnormal methylation, these deletions alter the activity of the *IGF2* and *H19* genes.

### Prostate cancer

**Russell-Silver syndrome**

Changes in methylation of the IC1 region are also responsible for some cases of Russell-Silver syndrome, a disorder characterized by slow growth before and after birth. The changes are different than those seen in Beckwith-Wiedemann syndrome (described above) and have the opposite effect on growth.

In Russell-Silver syndrome, the paternally inherited copy of the IC1 region often has too few methyl groups attached (hypomethylation). Hypomethylation of the IC1 region leads to a loss of *IGF2* gene activity and increased activity of the *H19* gene in many tissues. A loss of *IGF2* gene activity, which normally promotes growth, and an increase in *H19* gene activity, which restrains growth, together lead to poor growth and short stature in people with Russell-Silver syndrome.

### Wilms tumor

Changes in methylation of the IC1 region have also been found in some cases of Wilms tumor, a rare form of kidney cancer that occurs almost exclusively in children.

In some people with Wilms tumor, the maternally inherited copy of the IC1 region is methylated along with the paternally inherited copy. Abnormal methylation of the IC1 region leads to a loss of *H19* gene activity, which normally restrains cell growth, and increased *IGF2* gene activity in kidney cells. Increased *IGF2* gene activity raises insulin-like growth factor 2 protein production, which likely stimulates the growth of tumor cells in the kidney and prevents damaged cells from being destroyed. As this mechanism is similar to the one that causes Beckwith-Wiedemann syndrome (described above), it is thought that individuals with Wilms tumor caused by changes in IC1 methylation may later be diagnosed with Beckwith-Wiedemann syndrome.

In most cases, abnormal methylation of IC1 and subsequent changes in *IGF2* and *H19* gene activity are somatic, which means that they are acquired during a person's lifetime and present only in some tissues. Rarely, these changes are germline, which means they are present in all of the body's cells.

### Other cancers

Increased activity of the *IGF2* gene has been associated with many types of cancer. Normally, the *IGF2* gene undergoes genomic imprinting and only the copy inherited from a person's father is active. In some cancers, however, both the paternally inherited and the maternally inherited copies of the gene are active, increasing the amount of insulin-like growth factor 2 that cells can produce. This phenomenon, known as loss of imprinting (LOI), occurs during a person's lifetime in cells that
ultimately give rise to cancer. An increased amount of insulin-like growth factor 2 may stimulate the growth of tumor cells and prevent damaged cells from being destroyed.

Loss of imprinting of the IGF2 gene has been identified in several types of cancer. In some cases these cancers occur without any other related health problems, in other cases they occur in people with Beckwith-Wiedemann syndrome (described above). These include cancer of blood-forming cells (leukemia), a cancer of muscle tissue called rhabdomyosarcoma, a form of liver cancer called hepatoblastoma, and cancers of the breast, prostate, lung, and colon. In some types of cancer, increased levels of insulin-like growth factor 2 are associated with the growth and spread of tumors.

**Chromosomal Location**

Cytogenetic Location: 11p15.5, which is the short (p) arm of chromosome 11 at position 15.5

Molecular Location: base pairs 2,129,112 to 2,149,603 on chromosome 11 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (NCBI)

**Other Names for This Gene**

- C11orf43
- FLJ22066
- FLJ44734
- IGF-2
- IGF-II
- IGF2_HUMAN
- INSIGF
- insulin-like growth factor 2
- insulin-like growth factor 2 (somatomedin A)
- insulin-like growth factor II
- insulin-like growth factor type 2
• pp9974
• putative insulin-like growth factor II associated protein
• somatomedin A

Additional Information & Resources

Educational Resources
  https://www.ncbi.nlm.nih.gov/books/NBK9904/#A1014

Clinical Information from GeneReviews
• Beckwith-Wiedemann Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1394
• Silver-Russell Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1324
• Wilms Tumor Predisposition
  https://www.ncbi.nlm.nih.gov/books/NBK1294

Scientific Articles on PubMed
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  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28IGF2%5BTIAB%5D%29+OR
  +%28insulin-like+growth+factor+2%5BTIAB%5D%29+AND+english%5Bla
  %5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM
• H19/IGF2-IMPRINTING CONTROL REGION
  http://omim.org/entry/616186
• INSULIN-LIKE GROWTH FACTOR II
  http://omim.org/entry/147470

Research Resources
• Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_IGF2.html
• Cancer Genetics Web
  http://www.cancerindex.org/geneweb/IGF2.htm
• ClinVar
• HGNC Gene Symbol Report

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