



Chromosome 4

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 4, one copy inherited from each parent, form one of the pairs. Chromosome 4 spans about 191 million DNA building blocks (base pairs) and represents more than 6 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 4 likely contains 1,000 to 1,100 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body.

Health Conditions Related to Chromosomal Changes

The following chromosomal conditions are associated with changes in the structure or number of copies of chromosome 4.

Cancers

Changes in chromosome 4 have been identified in several types of human cancer. These genetic changes are somatic, which means they are acquired during a person's lifetime and are present only in certain cells. For example, rearrangements (translocations) of genetic material between chromosome 4 and several other chromosomes have been associated with leukemias, which are cancers of blood-forming cells.

A specific translocation involving chromosome 4 and chromosome 14 is commonly found in multiple myeloma, which is a cancer that starts in cells of the bone marrow. The translocation, which is written as $t(4;14)(p16;q32)$, abnormally fuses the *WHSC1* gene on chromosome 4 with part of another gene on chromosome 14. The fusion of these genes overactivates *WHSC1*, which appears to promote the uncontrolled growth and division of cancer cells.

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy is caused by genetic changes involving the long (q) arm of chromosome 4. This condition is characterized by muscle weakness and wasting (atrophy) that worsens slowly over time. It results from changes in a region of DNA known as D4Z4, located near the end of the chromosome at a position described as 4q35. The D4Z4 region consists of 11 to more than 100 repeated segments, each of which is about 3,300 DNA base pairs (3.3 kb) long. The entire D4Z4 region is normally hypermethylated, which means that it has a large number of methyl groups (consisting of one carbon atom and three hydrogen atoms) attached

to the DNA. Facioscapulohumeral muscular dystrophy results when the region is hypomethylated, with too few methyl groups attached. In facioscapulohumeral muscular dystrophy type 1 (FSHD1), hypomethylation occurs because the D4Z4 region is abnormally shortened (contracted), containing between 1 and 10 repeats instead of the usual 11 to 100 repeats. In facioscapulohumeral muscular dystrophy type 2 (FSHD2), hypomethylation most often results from mutations in a gene called *SMCHD1*, which normally hypermethylates the D4Z4 region.

The segment of the D4Z4 region closest to the end of chromosome 4 contains a gene called *DUX4*. Hypermethylation of the D4Z4 region normally keeps the *DUX4* gene turned off (silenced) in most adult cells and tissues. In people with facioscapulohumeral muscular dystrophy, hypomethylation of the D4Z4 region prevents the *DUX4* gene from being silenced in cells and tissues where it is usually turned off. Although little is known about the function of the *DUX4* gene when it is turned on (active), researchers believe that it influences the activity of other genes, particularly in muscle cells. It is unknown how abnormal activity of the *DUX4* gene damages or destroys these cells, leading to progressive muscle weakness and atrophy.

The *DUX4* gene is located next to a regulatory region of DNA known as a pLAM sequence, which is necessary for the production of the *DUX4* protein. Some copies of chromosome 4 have a functional pLAM sequence, while others do not. Copies of chromosome 4 with a functional pLAM sequence are described as 4qA or "permissive." Those without a functional pLAM sequence are described as 4qB or "non-permissive." Without a functional pLAM sequence, no *DUX4* protein is made. Because there are two copies of chromosome 4 in each cell, individuals may have two "permissive" copies of chromosome 4, two "non-permissive" copies, or one of each. Facioscapulohumeral muscular dystrophy can only occur in people who have at least one "permissive" copy of chromosome 4. Whether an affected individual has a contracted D4Z4 region or a *SMCHD1* gene mutation, the disease results only if a functional pLAM sequence is also present to allow *DUX4* protein to be produced.

PDGFRA-associated chronic eosinophilic leukemia

PDGFRA-associated chronic eosinophilic leukemia is caused by genetic abnormalities that involve the *PDGFRA* gene, a gene found on chromosome 4. This condition is a type of blood cell cancer characterized by an increased number of eosinophils, a type of white blood cell involved in allergic reactions.

The *PDGFRA* gene abnormalities are somatic mutations, which are mutations acquired during a person's lifetime that are present only in certain cells. The most common of these abnormalities is a deletion of genetic material from chromosome 4 that removes approximately 800 DNA building blocks (nucleotides) and brings together parts of two genes, *FIP1L1* and *PDGFRA*, creating the *FIP1L1-PDGFRA* fusion gene. Occasionally, through mechanisms other than deletion, genes other than *FIP1L1* are fused with the *PDGFRA* gene. Rarely, mutations that change single DNA building blocks in the *PDGFRA* gene (point mutations) cause this condition.

The protein produced from the *FIP1L1-PDGFR*A fusion gene (as well as other *PDGFR*A fusion genes) has the function of the *PDGFR*A protein, which stimulates signaling pathways inside the cell that control many important cellular processes, such as cell growth and division (proliferation) and cell survival. Unlike the normal *PDGFR*A protein, however, the fusion protein is constantly turned on (constitutively activated), which means the cells are always receiving signals to proliferate. Similarly, point mutations in the *PDGFR*A gene can result in a constitutively activated *PDGFR*A protein. When the *FIP1L1-PDGFR*A fusion gene or point mutations in the *PDGFR*A gene occur in blood cell precursors, the growth of eosinophils (and occasionally other blood cells) is poorly controlled, leading to *PDGFR*A-associated chronic eosinophilic leukemia. It is unclear why eosinophils are preferentially affected by this genetic change.

Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome is caused by a deletion of genetic material near the end of the short (p) arm of chromosome 4 at a position described as 4p16.3. The signs and symptoms of this condition are related to the loss of multiple genes from this part of the chromosome. The size of the deletion varies among affected individuals; studies suggest that larger deletions tend to result in more severe intellectual disability and physical abnormalities than smaller deletions.

The region of chromosome 4 that is deleted most often in people with Wolf-Hirschhorn syndrome is known as Wolf-Hirschhorn syndrome critical region 2 (WHSCR-2). This region contains several genes, some of which are known to play important roles in early development. A loss of these genes leads to developmental delay, a distinctive facial appearance, and other characteristic features of the condition. Scientists are working to identify additional genes at the end of the short arm of chromosome 4 that contribute to the characteristic features of Wolf-Hirschhorn syndrome.

Other chromosomal conditions

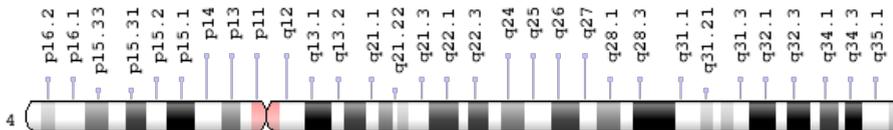
Some deletions of genetic material from the short (p) arm of chromosome 4 do not involve the critical region WHSCR-2. These deletions cause signs and symptoms that are distinct from those of Wolf-Hirschhorn syndrome, including mild intellectual disability and, in some cases, rapid (accelerated) growth. People with this type of deletion usually do not have seizures.

Trisomy 4 occurs when cells have three copies of chromosome 4 instead of the usual two copies. Full trisomy 4, which occurs when all of the body's cells contain an extra copy of chromosome 4, is not compatible with life. A similar but somewhat less severe condition called mosaic trisomy 4 occurs when only some of the body's cells have an extra copy of chromosome 4. The signs and symptoms of mosaic trisomy 4 vary widely and can include heart defects, abnormalities of the fingers and toes, and other birth defects. Mosaic trisomy 4 is very rare; only a few cases have been reported.

Other changes in the number or structure of chromosome 4 can have a variety of effects including delayed growth and development, intellectual disability, distinctive facial features, heart defects, and other medical problems. Changes involving chromosome 4 include an extra piece of the chromosome in each cell (partial trisomy 4), a missing segment of the chromosome in each cell (partial monosomy 4), and a circular structure called a ring chromosome 4. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

Chromosome Diagram

Geneticists use diagrams called idiograms as a standard representation for chromosomes. Idiograms show a chromosome's relative size and its banding pattern, which is the characteristic pattern of dark and light bands that appears when a chromosome is stained with a chemical solution and then viewed under a microscope. These bands are used to describe the location of genes on each chromosome.



Credit: Genome Decoration Page/NCBI

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Chromosome
<https://medlineplus.gov/ency/article/002327.htm>

Additional NIH Resources

- Genes and Disease
<https://www.ncbi.nlm.nih.gov/books/NBK22266/>
- National Human Genome Research Institute: Chromosome Abnormalities
<https://www.genome.gov/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet>

Clinical Information from GeneReviews

- Facioscapulohumeral Muscular Dystrophy
<https://www.ncbi.nlm.nih.gov/books/NBK1443>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Chromosomes,+Human,+Pair+4%5BMAJR%5D%29+AND+%28%284%5BTI%5D%29+OR+%284p%5BTI%5D%29+OR+%284q%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- MYELOMA, MULTIPLE
<http://omim.org/entry/254500>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology: Chromosome 4
http://atlasgeneticsoncology.org/Indexbychrom/idxa_4.html
- Atlas of Genetics and Cytogenetics in Oncology and Haematology: t(4;14)(p16;q32)
<http://atlasgeneticsoncology.org/Anomalies/t04142059ID2059.html>
- Cancer Genetics Web
<http://www.cancerindex.org/geneweb/clinkc04.htm>
- Database of Genomic Variants
http://projects.tcag.ca/variation/cgi-bin/tbrowse/tbrowse?source=hg17&table=Locus&show=table&keyword=&flop=AND&fcol=_C19&fcomp==&fkwd=chr4&cols=
- Ensembl Human Map View
http://www.ensembl.org/Homo_sapiens/Location/Chromosome?chr=4;r=4:1-190214555
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<https://www.nature.com/articles/nature03466.pdf>
- U.S. Department of Energy: Human Genome Project Information Archive
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