Chromosome 22

Description

Humans normally have 46 chromosomes (23 pairs) in each cell. Two copies of chromosome 22, one copy inherited from each parent, form one of the pairs. Chromosome 22 is the second smallest human chromosome, spanning more than 51 million DNA building blocks (base pairs) and representing between 1.5 and 2 percent of the total DNA in cells.

In 1999, researchers working on the Human Genome Project announced they had determined the sequence of base pairs that make up this chromosome. Chromosome 22 was the first human chromosome to be fully sequenced.

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 22 likely contains 500 to 600 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 22.

22q11.2 deletion syndrome

22q11.2 deletion syndrome is a disorder involving heart defects, an opening in the roof of the mouth (a cleft palate), distinctive facial features, low calcium levels, and an increased risk of behavioral problems and mental illness such as schizophrenia (described below). Most people with 22q11.2 deletion syndrome are missing about 3 million base pairs on one copy of chromosome 22 in each cell. The deletion occurs near the middle of the chromosome at a location designated as q11.2. This region contains 30 to 40 genes, but many of these genes have not been well characterized. A small percentage of affected individuals have shorter deletions in the same region.

The loss of a particular gene, *TBX1*, is thought to be responsible for many of the physical features characteristic of 22q11.2 deletion syndrome. Additional genes in the deleted region likely contribute to the varied signs and symptoms of 22q11.2 deletion syndrome.

22q11.2 duplication

22q11.2 duplication is caused by an extra copy of some genetic material at position q11.2 on chromosome 22. In most cases, this extra genetic material consists of a sequence of about 3 million base pairs, also written as 3 megabases (Mb). This sequence is the same one that is missing in 22q11.2 deletion syndrome (described above). A small percentage of affected individuals have a shorter duplication in the same region. The duplication affects one of the two copies of chromosome 22 in each cell. Researchers are working to determine the genes that may contribute to the developmental delay and other problems that affect some people with this duplication.

22q13.3 deletion syndrome

22q13.3 deletion syndrome, which is also commonly known as Phelan-McDermid syndrome, is caused by a deletion near the end of the long (q) arm of chromosome 22. A ring chromosome 22 can also cause 22q13.3 deletion syndrome. A ring chromosome is a circular structure that occurs when a chromosome breaks in two places, the tips of the chromosome are lost, and the broken ends fuse together. People with ring chromosome 22 have one copy of this abnormal chromosome in some or all of their cells. Researchers believe that several critical genes near the end of the q arm of chromosome 22 are lost when the ring chromosome 22 forms. If the break point on the long arm is at chromosome position 22q13.3, people with ring chromosome 22 will experience similar signs and symptoms as those with a simple deletion.

The signs and symptoms of 22q13.3 deletion syndrome are probably related to the loss of multiple genes at the end of chromosome 22. The size of the deletion varies among affected individuals. The loss of a particular gene, *SHANK3*, is thought to be responsible for many of the characteristic features of 22q13.3 deletion syndrome, such as developmental delay, intellectual disability, and absent or severely delayed speech. Additional genes in the deleted region likely contribute to the signs and symptoms of 22q13.3 deletion syndrome.

Chronic myeloid leukemia

A rearrangement (translocation) of genetic material between chromosomes 9 and 22 causes a type of cancer of blood-forming cells called chronic myeloid leukemia. This slow-growing cancer leads to an overproduction of abnormal white blood cells. Common features of the condition include excessive tiredness (fatigue), fever, weight loss, and an enlarged spleen.

The translocation involved in this condition, written as t(9;22), fuses part of the *ABL1* gene from chromosome 9 with part of the *BCR* gene from chromosome 22, creating an abnormal fusion gene called *BCR-ABL1*. The abnormal chromosome 22, containing a piece of chromosome 9 and the fusion gene, is commonly called the Philadelphia chromosome. The translocation is acquired during a person's lifetime and is present only in the abnormal blood cells. This type of genetic change, called a somatic mutation, is not inherited.

The protein produced from the *BCR-ABL1* gene signals cancer cells to continue dividing

abnormally and prevents them from self-destructing, which leads to overproduction of the abnormal cells and a shortage of normal blood cells.

The Philadelphia chromosome also has been found in some cases of rapidly progressing blood cancers known as acute leukemias. It is likely that the form of blood cancer that develops is influenced by the type of blood cell that acquires the mutation and other genetic changes that occur. The presence of the Philadelphia chromosome provides a target for molecular therapies.

Dermatofibrosarcoma protuberans

A rearrangement (translocation) of genetic material between chromosomes 17 and 22, written as t(17;22), causes a rare type of skin cancer known as dermatofibrosarcoma protuberans. This translocation fuses part of the *PDGFB* gene from chromosome 22 with part of the *COL1A1* gene from chromosome 17. The translocation is found on one or more extra chromosomes that can be either linear or circular. When circular, the extra chromosomes are known as supernumerary ring chromosomes. This mutation is acquired during a person's lifetime and is present only in certain cells. This type of genetic change, called a somatic mutation, is not inherited.

The fused *COL1A1-PDGFB* gene provides instructions for making a combined (fusion) protein that ultimately functions like the active PDGFB protein. In the translocation, the *PDGFB* gene loses the part of its DNA that limits its activity, and production of the COL1A1-PDGFB fusion protein is controlled by *COL1A1* gene sequences. As a result, the gene fusion leads to the production of a larger amount of active PDGFB protein than normal. Active PDGFB protein signals for cell growth and division (proliferation) and maturation (differentiation). Excess PDGFB protein abnormally stimulates cells to proliferate and differentiate, leading to the tumor formation seen in dermatofibrosarcoma protuberans.

Emanuel syndrome

Emanuel syndrome is caused by the presence of extra genetic material from chromosome 11 and chromosome 22 in each cell. In addition to the usual 46 chromosomes, people with Emanuel syndrome have an extra (supernumerary) chromosome consisting of a piece of chromosome 11 attached to a piece of chromosome 22. The extra chromosome is known as a derivative 22 or der(22) chromosome.

People with Emanuel syndrome typically inherit the der(22) chromosome from an unaffected parent. The parent carries a chromosomal rearrangement between chromosomes 11 and 22 called a balanced translocation. No genetic material is gained or lost in a balanced translocation, so these chromosomal changes usually do not cause any health problems. As this translocation is passed to the next generation, it can become unbalanced. Individuals with Emanuel syndrome inherit an unbalanced translocation between chromosomes 11 and 22 in the form of a der(22) chromosome. These individuals have two normal copies of chromosome 11, two normal copies of chromosome 22, and extra genetic material from the der(22) chromosome.

As a result of the extra chromosome, people with Emanuel syndrome have three copies of some genes in each cell instead of the usual two copies. The excess genetic material disrupts the normal course of development, leading to intellectual disability and birth defects. Researchers are working to determine which genes are included on the der(22) chromosome and what role these genes play in development.

Ewing sarcoma

Translocations involving chromosome 22 are also involved in a type of cancerous tumor known as Ewing sarcoma. These tumors develop in the bones or soft tissues, such as cartilage and nerves. The most common translocation, t(11;22), fuses part of the *EWSR1* gene from chromosome 22 with part of the *FLI1* gene from chromosome 11, creating the *EWSR1/FLI1* fusion gene. Translocations that fuse the *EWSR1* gene with other genes that are related to the *FLI1* gene can also cause Ewing sarcomas, although these alternative translocations are relatively uncommon. The mutations that cause these cancers are acquired during a person's lifetime and are present only in tumor cells. This type of genetic change, called a somatic mutation, is not inherited.

The protein produced from the *EWSR1/FLI1* fusion gene, called EWS/FLI, has functions of the protein products of both genes. The FLI protein, produced from the FLI1 gene, attaches (binds) to DNA and regulates an activity called transcription, which is the first step in the production of proteins from genes. The FLI protein controls the growth and development of some cell types by regulating the transcription of certain genes. The EWS protein, produced from the EWSR1 gene, also regulates transcription. The EWS/FLI protein has the DNA-binding function of the FLI protein as well as the transcription regulation function of the EWS protein. It is thought that the EWS/FLI protein turns the transcription of a variety of genes on and off abnormally. This dysregulation of transcription leads to uncontrolled growth and division (proliferation) and abnormal maturation and survival of cells, causing tumor development.

Opitz G/BBB syndrome

A deletion in one copy of chromosome 22 can cause Opitz G/BBB syndrome. This condition causes several abnormalities along the midline of the body, including widely spaced eyes (ocular hypertelorism), difficulty breathing or swallowing, brain malformations, distinct facial features, and genital abnormalities in males. The deletion that causes Opitz G/BBB syndrome is in the same area as the deletion that causes 22q11.2 deletion syndrome (described above), so Opitz G/BBB is often considered part of 22q11.2 deletion syndrome. It is not yet known which deleted genes cause the signs and symptoms of Opitz G/BBB syndrome.

Schizophrenia

A small percentage of individuals with schizophrenia have a small deletion (microdeletion) in a region of chromosome 22 called 22q11. Schizophrenia is a mental health disorder that affects a person's thinking, sense of self, and perceptions. The 22q11 region contains several genes that are thought to affect schizophrenia risk. Loss of one or more of these genes may affect the brain in ways that increase the risk of

developing this disorder. However, the relationships between these gene losses and the development of the disorder are not well understood.

In addition to schizophrenia, some people with this deletion have additional signs and symptoms comprising a condition called 22q11.2 deletion syndrome (described above).

22q11 microdeletions are among many factors under study to help explain the causes of schizophrenia. A large number of genetic and environmental factors, most of which remain unknown, likely contribute to the risk of developing this complex condition.

Other chromosomal conditions

Other changes in the number or structure of chromosome 22 can have a variety of effects. Intellectual disability, delayed development, delayed or absent speech, distinctive facial features, and behavioral problems are common features. Frequent changes to chromosome 22 include an extra piece of the chromosome in each cell (partial trisomy), a missing segment of the chromosome in each cell (partial monosomy), and a ring chromosome 22. Translocations of genetic material between chromosomes can also lead to extra or missing material from chromosome 22. The most common of these translocations involves chromosomes 11 and 22.

Cat-eye syndrome is a rare disorder most often caused by a chromosomal change called an inverted duplicated 22. In people with this condition, each cell has at least one small extra chromosome made up of genetic material from chromosome 22 that has been abnormally duplicated. The extra genetic material causes the characteristic signs and symptoms of cat-eye syndrome, including an eye abnormality called an iris coloboma (a gap or split in the colored part of the eye), small skin tags or pits in front of the ear, unusually formed ears, heart defects, kidney problems, malformations of the anus, and, in some cases, delayed development.

Additional Information & Resources

Additional NIH Resources

- National Human Genome Research Institute: Chromosome Abnormalities (https://www.genome.gov/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Chromosomes,+Human,+Pair+22%5BMAJR%5D%29+AND+%28Chromosome+22%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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