Chromosome 16

Subjects: Genetics & Heredity
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Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 16, one copy inherited from each parent, form one of the pairs.

Keywords: chromosomes & mtDNA

1. Introduction

Chromosome 16 spans more than 90 million DNA building blocks (base pairs) and represents almost 3 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 16 likely contains 800 to 900 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body.

2. Health Conditions Related to Chromosomal Changes

2.1. 16p11.2 deletion syndrome

16p11.2 deletion syndrome is caused by a deletion of about 600,000 base pairs, also written as 600 kilobases (kb), at position 11.2 on the short (p) arm of chromosome 16. This deletion affects one of the two copies of chromosome 16 in each cell. The 600 kb region contains more than 25 genes, and in many cases little is known about their function. Researchers are working to determine how the missing genes contribute to the features of 16p11.2 deletion syndrome, which include delayed development; intellectual disability; and autism spectrum disorder, which affects communication and social interaction. Obesity is another common feature of 16p11.2 deletion syndrome; individuals with the deletion also have an increased risk of seizures. Most people with the deletion have some of these signs and symptoms, but others do not. Although some people have this deletion without serious consequences, they can still pass it to their children, who may be more severely affected.

2.2. 16p11.2 duplication

A 16p11.2 duplication is an extra copy of the same 600 kb segment of chromosome 16 that is missing in 16p11.2 deletion syndrome (described above). A 16p11.2 duplication may result in similar signs and symptoms as the deletion in some affected individuals, including features of autism spectrum disorder; however, being underweight is common in people with the duplication, while obesity often occurs with the deletion.

The 16p11.2 duplication appears to have a milder effect than the deletion, with a higher proportion of individuals with this chromosomal change showing no apparent problems. These individuals can still pass along the duplication to their children, who may have signs and symptoms related to the chromosomal change. Researchers are working to determine how the extra genetic material contributes to the features that occur in some people with a 16p11.2 duplication, and why duplication or deletion of the same chromosomal region can have some similar effects.

2.3. 16p12.2 microdeletion

A small amount of missing genetic material on the p arm of chromosome 16 causes a condition called 16p12.2 microdeletion, which is associated with physical and developmental abnormalities in some affected individuals. People with this chromosomal abnormality are missing a sequence of about 520,000 base pairs, also written as 520 kb, at position p12.2 on chromosome 16. The deleted region contains seven genes. This deletion affects one of the two copies of chromosome 16 in each cell.

The signs and symptoms that can result from a 16p12.2 microdeletion are generally related to the loss of one or more genes in this region. However, it is unclear which missing genes contribute to specific features that can occur in the disorder. Because some people with a 16p12.2 microdeletion have no obvious signs or symptoms (a situation called incomplete penetrance), researchers believe that other genetic or environmental factors may also be involved. In particular, studies indicate that individuals with a 16p12.2 microdeletion who have neurological or behavioral problems often have an additional, larger deletion or duplication affecting another chromosome. Small duplications of genetic material that occur near the 16p12.2 microdeletion may also contribute to the features associated with this condition.

2.4. Alveolar capillary dysplasia with misalignment of pulmonary veins

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a disorder that affects the development of blood vessels in the lungs. It can be caused by a deletion of genetic material on chromosome 16 in a region known as 16q24.1. This region includes several genes, including the *FOXF1* gene. The protein produced from the *FOXF1* gene is a transcription factor, which means that it attaches (binds) to specific regions of DNA and helps control the activity of many other genes. The FOXF1 protein helps regulate the development of the lungs and the gastrointestinal tract. Genetic changes that result in a nonfunctional FOXF1 protein interfere with the development of pulmonary blood vessels and cause ACD/MPV. Affected infants may also have gastrointestinal abnormalities.

Researchers suggest that deletions resulting in the loss of other genes in this region of chromosome 16 probably cause the additional abnormalities seen in some infants with this disorder. Like *FOXF1*, these genes also provide instructions for making transcription factors that regulate development of various body systems before birth.

2.5. Core binding factor acute myeloid leukemia

Another type of blood cancer known as core binding factor acute myeloid leukemia (CBF-AML) is associated with rearrangements of genetic material on chromosome 16. The most common of these rearrangements is an inversion of a region of chromosome 16 (written as inv(16)). An inversion involves breakage of the chromosome in two places; the resulting piece of DNA is reversed and reinserted into the chromosome. Less commonly, a translocation occurs between the two copies of chromosome 16 (written as t(16;16)). Both types of genetic rearrangement result in the fusion of two genes found on chromosome 16, *CBFB* and *MYH11*. These genetic changes are associated with 5 to 8 percent of cases of AML in adults. These mutations are acquired during a person's lifetime and are present only in certain cells. This type of genetic change, called a somatic mutation, is not inherited.

The protein produced from the normal *CBFB* gene interacts with another protein called RUNX1 to form a complex called core binding factor (CBF). This complex attaches to specific areas of DNA and turns on genes that are involved in the development of blood cells. The protein produced from the fusion gene, CBFβ-MYH11, can still bind to RUNX1. However, the function of CBF is impaired. The presence of CBFβ-MYH11 may block binding of CBF to DNA, impairing its ability to control gene activity. Alternatively, the MYH11 portion of the fusion protein may interact with other proteins that prevent the complex from controlling gene activity. The change in gene activity blocks the maturation (differentiation) of blood cells, which leads to the production of abnormal, immature white blood cells called myeloid blasts and to a shortage of normal, mature blood cell types. However, one or more additional genetic changes are typically needed for the myeloid blasts to develop into cancerous leukemia cells.

2.6. Rubinstein-Taybi syndrome

Some cases of severe Rubinstein-Taybi syndrome (sometimes known as chromosome 16p13.3 deletion syndrome) have resulted from a deletion of genetic material from the p arm of chromosome 16. When this deletion occurs in all of the body's cells, it can cause serious complications such as a failure to gain weight and grow at the expected rate (failure to thrive) and an increased risk of life-threatening infections. Affected individuals also have many of the typical features of Rubinstein-Taybi syndrome, including intellectual disability, distinctive facial features, and broad thumbs and first toes. Infants born with the severe form of this disorder usually survive only into early childhood.

Several genes are missing as a result of this deletion in the short arm of chromosome 16. The deleted region includes the *CREBBP* gene, which is often mutated or missing in people with the typical features of Rubinstein-Taybi syndrome. Researchers believe that the loss of additional genes in this region probably accounts for the serious complications associated with severe Rubinstein-Taybi syndrome. However, a few studies indicate that deletions of multiple genes in the p arm of chromosome 16 do not always cause severe signs and symptoms.

2.7. Cancers

Changes in the structure of chromosome 16 are associated with several types of cancer. These genetic changes are somatic, which means they are acquired during a person's lifetime and are present only in certain cells. In some cases, chromosomal rearrangements called translocations disrupt the region of chromosome 16 that contains the *CREBBP* gene. The protein produced from this gene normally plays a role in regulating cell growth and division, which helps prevent the development of cancers.

Researchers have found a translocation between chromosome 8 and chromosome 16 that disrupts the *CREBBP* gene in some people with a cancer of blood-forming cells called acute myeloid leukemia (AML). Another translocation involving the *CREBBP* gene, which rearranges pieces of chromosomes 11 and 16, has been found in some people who have undergone cancer treatment. This chromosomal change is associated with the later development of AML and two other cancers of blood-forming tissues (chronic myeloid leukemia and myelodysplastic syndrome). These are sometimes described as treatment-related cancers because the translocation between chromosomes 11 and 16 occurs following chemotherapy for other forms of cancer.

2.8. Other chromosomal conditions

Trisomy 16 occurs when cells have three copies of chromosome 16 instead of the usual two copies. Full trisomy 16, which occurs when all of the body's cells contain an extra copy of chromosome 16, causes serious health problems. Most affected individuals die before or shortly after birth, although some have lived for weeks or months with intensive medical support. A similar but less severe condition called mosaic trisomy 16 occurs when only some of the body's cells have an extra copy of chromosome 16. The signs and symptoms of mosaic trisomy 16 vary widely and can include slow growth before birth (intrauterine growth retardation), delayed development, and heart defects.

Other changes in the number or structure of chromosome 16 can have a variety of effects. Intellectual disability, delayed growth and development, distinctive facial features, weak muscle tone (hypotonia), heart defects, and other medical problems are common. Frequent changes to chromosome 16 include an extra segment of the short (p) or long (q) arm of the chromosome in each cell (partial trisomy 16p or 16q) and a missing segment of the long arm of the chromosome in each cell (partial monosomy 16q).

For example, a region of DNA on chromosome 16 that includes the *CREBBP* gene is copied (duplicated) in some people. This genetic change causes a condition called chromosome 16p13.3 duplication syndrome, which is characterized by intellectual disability, distinctive facial features, abnormal thumbs, and rigid joints (arthrogryposis). Some affected individuals also have abnormalities of the heart, genitals, roof of the mouth, or the eyes.

While other genes can be included in the duplicated region, depending on its size, research shows that the *CREBBP* gene is most likely responsible for the characteristic signs and symptoms of chromosome 16p13.3 duplication syndrome. Researchers suspect that an extra copy of the *CREBBP* gene leads to the production of excess CREB binding protein and an increase in protein function. The resulting changes in gene transcription and protein production likely alter development of various systems, causing the signs and symptoms of chromosome 16p13.3 duplication syndrome.

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