Chromosome 15

Subjects: Genetics & Heredity
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Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 15, one copy inherited from each parent, form one of the pairs.

Keywords: chromosomes & mtDNA

1. Introduction

Chromosome 15 spans more than 102 million DNA building blocks (base pairs) and represents more than 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 15 likely contains 600 to 700 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. 15q11-q13 duplication syndrome

Duplication of a region of the long (q) arm of chromosome 15 can result in 15q11-q13 duplication syndrome (dup15q syndrome), a condition whose features can include weak muscle tone (hypotonia), intellectual disability, recurrent seizures (epilepsy), characteristics of autism spectrum disorder affecting communication and social interaction, and other behavioral problems.

Dup15q syndrome is caused by the presence of at least one extra copy of a region of chromosome 15 called 15q11.2-q13.1. This region is also called the Prader-Willi/Angelman critical region (PWACR) because genetic changes in it are also involved in conditions called Prader-Willi syndrome and Angelman syndrome (described below). Dup15q syndrome arises only if the chromosome abnormality occurs on the copy of the chromosome inherited from the mother (the maternal copy). People normally inherit one copy of chromosome 15 from each parent. However, some genes on this chromosome, including some of those in the 15q11.2-q13.1 region, are turned on (active) only on the maternal copy. This parent-specific gene activation results from a phenomenon called genomic imprinting.

The most common chromosome abnormality that leads to 15q11.2-q13.1 duplication, occurring in about 80 percent of people with dup15q syndrome, is called an isodicentric chromosome 15. An isodicentric chromosome contains mirror-image segments of genetic material and has two constriction points (centromeres), rather than one centromere as in normal chromosomes. In people with an isodicentric chromosome 15, cells have the usual two copies of chromosome 15 plus the two duplicated copies of the segment of genetic material in the isodicentric chromosome, for a total of four copies of the duplicated segment.

In about 20 percent of cases of dup15q syndrome, the duplication occurs on the long (q) arm of one of the two copies of chromosome 15 in each cell; this situation is called an interstitial duplication. In these cases, cells have two copies of chromosome 15, one of which has an extra copy of the segment of genetic material, for a total of three copies of the duplicated segment.

In all cases of dup15q syndrome, the duplicated genetic material results in extra copies of certain genes involved in development. This extra genetic material disrupts normal development, causing the characteristic features of this disorder. People with dup15q syndrome resulting from an interstitial duplication often have milder signs and symptoms than those in whom the disorder results from an isodicentric chromosome 15.

2.2. 15q13.3 microdeletion

15q13.3 microdeletion is a chromosomal change in which a small piece of chromosome 15 is deleted in each cell. The deletion occurs on the q arm of the chromosome at a position designated q13.3. Most people with a 15q13.3 microdeletion are missing a sequence of about 2 million DNA base pairs, also written as 2 megabases (Mb). The exact size of the deleted region varies, but it typically contains at least six genes. It is unclear how a loss of these genes increases the risk of intellectual disability, seizures, behavioral problems, and psychiatric disorders in some individuals with a 15q13.3 microdeletion.

Other people with a 15q13.3 microdeletion have no obvious signs or symptoms related to the chromosomal change. In these individuals, the microdeletion is often detected when they undergo genetic testing because they have an affected relative. It is unknown why 15q13.3 microdeletion causes cognitive and behavioral problems in some individuals but few or no health problems in others. Researchers believe that additional genetic or environmental factors may be involved.

2.3. 15q24 microdeletion

15q24 microdeletion is a chromosomal change in which a small piece of chromosome 15 is deleted in each cell. Specifically, affected individuals are missing between 1.7 Mb and 6.1 Mb of DNA at position q24 on chromosome 15. The exact size of the deletion varies, but all individuals are missing the same 1.2 Mb region. This region contains several genes that are thought to be important for normal development. It is unclear how a loss of these genes leads to intellectual disability, distinctive facial features, and other abnormalities often seen in people with a 15q24 microdeletion.

2.4. Acute promyelocytic leukemia

A type of blood cancer known as acute promyelocytic leukemia is caused by a rearrangement (translocation) of genetic material between chromosomes 15 and 17. This translocation, written as t(15;17), fuses part of the *PML* gene from chromosome 15 with part of the *RARA* gene from chromosome 17. 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 t(15;17) translocation is called a balanced reciprocal translocation because the pieces of chromosome are exchanged with each other (reciprocal) and no genetic material is gained or lost (balanced). The protein produced from this fused gene is known as PML-RARα.

The PML-RARα protein functions differently than the protein products from the normal *PML* and *RARA* genes. The *PML* gene on chromosome 15 provides instructions for a protein that acts as a tumor suppressor, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way. The PML protein blocks cell growth and division (proliferation) and induces self-destruction (apoptosis) in combination with other proteins. The *RARA* gene on chromosome 17 provides instructions for making a transcription factor called the retinoic acid receptor alpha (RARα). A transcription factor is a protein that attaches (binds) to specific regions of DNA and helps control the activity of particular genes. Normally, the RARα protein controls the activity (transcription) of genes important for the maturation (differentiation) of immature white blood cells beyond a particular stage called the promyelocyte. The PML-RARα protein interferes with the normal function of both the PML and the RARα proteins. As a result, blood cells are stuck at the promyelocyte stage, and they proliferate abnormally. Excess promyelocytes accumulate in the bone marrow and normal white blood cells cannot form, leading to acute promyelocytic leukemia.

2.5. Angelman syndrome

Angelman syndrome results from a loss of gene activity (expression) in a specific part of chromosome 15 in each cell. This region is located on the q arm of the chromosome and is designated 15q11-q13. This region contains a gene called *UBE3A* that, when mutated or absent, likely causes the characteristic neurologic features of Angelman syndrome.

People normally inherit one copy of the *UBE3A* gene from each parent, and both copies of this gene are active in many of the body's tissues. In certain areas of the brain, however, only the copy inherited from a person's mother (the maternal copy) is active. This parent-specific gene activation results from a phenomenon called genomic imprinting. If the maternal copy is lost because of a chromosomal change or a gene mutation, a person will have no working copies of the *UBE3A* gene in some parts of the brain.

In most cases (about 70 percent), Angelman syndrome results from a deletion in the maternal copy of chromosome 15. This chromosomal change deletes the region of chromosome 15 that includes the *UBE3A* gene. Because the copy of the *UBE3A* gene inherited from a person's father (the paternal copy) is normally inactive in certain parts of the brain, a deletion in the maternal chromosome 15 leaves no active copies of the *UBE3A* gene in these brain regions.

In 3 percent to 7 percent of cases of Angelman syndrome, the condition results when a person inherits two copies of chromosome 15 from his or her father instead of one copy from each parent. This phenomenon is called paternal uniparental disomy (UPD). People with paternal UPD for chromosome 15 have two copies of the *UBE3A* gene, but they are both inherited from the father and are therefore inactive in the brain.

About 10 percent of cases of Angelman syndrome are caused by a mutation in the *UBE3A* gene, and another 3 percent results from a defect in the DNA region that controls the activation of the *UBE3A* gene and other genes on the maternal copy of chromosome 15. In a small percentage of cases, Angelman syndrome is caused by a chromosomal rearrangement (translocation) or by a mutation in a gene other than *UBE3A*. These genetic changes abnormally inactivate the *UBE3A* gene.

2.6. Prader-Willi syndrome

Prader-Willi syndrome is caused by a loss of active genes in a region of chromosome 15. This region is located on the q arm of the chromosome and is designated 15q11-q13. It is the same part of chromosome 15 that is usually affected in people with Angelman syndrome, although different genes are associated with the two disorders. People can have either Prader-Willi syndrome or Angelman syndrome, but they typically cannot have both.

People normally inherit one copy of chromosome 15 from each parent. Some genes on this chromosome are turned on (active) only on the copy inherited from a person's father (the paternal copy). This parent-specific gene activation results from a phenomenon called genomic imprinting.

In about 70 percent of cases, Prader-Willi syndrome occurs when the 15q11-q13 region of the paternal chromosome 15 is deleted in each cell. A person with this chromosomal change will be missing certain critical genes in this region because the genes on the paternal copy have been deleted, and the genes on the maternal copy are turned off (inactive). Researchers are working to identify which missing genes are associated with the characteristic features of Prader-Willi syndrome.

In about 25 percent of cases, people with Prader-Willi syndrome inherit two copies of chromosome 15 from their mother instead of one copy from each parent. This phenomenon is called maternal UPD. A person with two maternal copies of chromosome 15 will have no active copies of certain genes in the 15q11-q13 region.

In a small percentage of cases, Prader-Willi syndrome is caused by a chromosomal rearrangement called a translocation. Rarely, the condition results from a mutation or other defect that abnormally inactivates genes on the paternal copy of chromosome 15.

2.7. Sensorineural deafness and male infertility

Sensorineural deafness and male infertility is caused by a deletion of genetic material on the q arm of chromosome 15. The symptoms of sensorineural deafness and male infertility are related to the loss of multiple genes in this region. The size of the deletion varies among affected individuals. Researchers have determined that the loss of a particular gene on chromosome 15, *STRC*, is responsible for hearing loss in affected individuals. The loss of another gene, *CATSPER2*, in the same region of chromosome 15 is responsible for sperm abnormalities, which lead to an inability to father children (infertility) in affected males. Researchers are working to determine how the loss of additional genes in the deleted region affects people with sensorineural deafness and male infertility.

2.8. Other chromosomal conditions

Other changes in the number or structure of chromosome 15 can cause intellectual disability, delayed growth and development, hypotonia, and characteristic facial features. These changes include an extra copy of part of chromosome 15 in each cell (partial trisomy 15), a missing segment of the chromosome in each cell (partial monosomy 15), and a circular structure called ring chromosome 15. A ring chromosome occurs when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

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