

Chromosome 17

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Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 17, one copy inherited from each parent, form one of the pairs.

chromosomes & mtDNA

1. Introduction

Chromosome 17 spans about 83 million DNA building blocks (base pairs) and represents between 2.5 and 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 17 likely contains 1,100 to 1,200 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. 17q12 deletion syndrome

17q12 deletion syndrome is a condition that results from the deletion of a small piece of chromosome 17 in each cell. Signs and symptoms of 17q12 deletion syndrome can include abnormalities of the kidneys and urinary system, a form of diabetes called maturity-onset diabetes of the young type 5 (MODY5), delayed development, intellectual disability, and behavioral or psychiatric disorders. Some females with this chromosomal change have Mayer-Rokitansky-Küster-Hauser syndrome, which is characterized by underdevelopment or absence of the vagina and uterus. Features associated with 17q12 deletion syndrome vary widely, even among affected members of the same family.

Most people with 17q12 deletion syndrome are missing about 1.4 million DNA building blocks (base pairs), also written as 1.4 megabases (Mb), on the long (q) arm of the chromosome at a position designated q12. It is the same region of chromosome 17 that is abnormally copied (duplicated) in people with a 17q12 duplication (described below). This chromosome segment is surrounded by short, repeated sequences of DNA that make it prone to rearrangement during cell division. The rearrangement can lead to missing or extra copies of DNA at 17q12.

The segment that is most often deleted in people with 17q12 deletion syndrome includes 15 genes. Some of the features associated with the condition likely result from the loss of two of these genes, *HNF1B* and *LHX1*. Studies suggest that a loss of one copy of the *HNF1B* gene in each cell causes the kidney and urinary tract abnormalities, as well as diabetes. Missing one copy of *LHX1* is thought to contribute to intellectual disability, behavioral and psychiatric conditions, and Mayer-Rokitansky-Küster-Hauser syndrome. The loss of other genes in the deleted region may also influence the signs and symptoms that can occur in 17q12 deletion syndrome.

2.2. 17q12 duplication

17q12 duplication is a chromosomal change in which a small piece of chromosome 17 is copied abnormally in each cell. Signs and symptoms related to this duplication vary significantly, even among members of the same family. Some individuals with the duplication have no apparent signs or symptoms, or the features are very mild. Other individuals can have intellectual disability, delayed development, and a wide range of physical abnormalities.

Most people with 17q12 duplications have an extra copy of about 1.4 Mb of DNA at position q12 on chromosome 17. It is the same region of chromosome 17 that is deleted in people with 17q12 deletion syndrome (described above). This chromosome segment is prone to rearrangement during cell division, which can lead to extra or missing copies of DNA at 17q12.

The duplicated segment of 17q12 includes at least 15 genes. It is unclear which of these genes, when present in more than one copy, contribute to intellectual disability, delayed development, and other features that can be associated with a 17q12 duplication. Because some people with this duplication have no obvious intellectual or physical problems, researchers suspect that additional genetic factors may influence whether a person has signs and symptoms related to the chromosomal change.

2.3. 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-RAR α .

The PML-RAR α protein functions differently than the protein products from the normal *PML* and *RARA* genes. The *RARA* gene on chromosome 17 provides instructions for making a transcription factor called the retinoic acid receptor alpha (RAR α). A transcription factor is a protein that attaches (binds) to specific regions of DNA and helps control the activity (transcription) of particular genes. Normally, the RAR α protein controls the activity of genes important for the maturation (differentiation) of immature white blood cells beyond a particular stage called the promyelocyte. 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 PML-RAR α protein interferes with the normal function of both the PML and the RAR α 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.

2.4. Charcot-Marie-Tooth disease

Duplication of a small piece of chromosome 17 at position p12 that includes the *PMP22* gene causes most cases of a disorder called Charcot-Marie-Tooth disease. When this disorder is caused by changes affecting the *PMP22* gene, it is called Charcot-Marie-Tooth disease type 1A, or CMT1A. Charcot-Marie-Tooth disease damages the peripheral nerves, which connect the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound. Peripheral nerve damage can result in alteration or loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands.

The protein produced from the *PMP22* gene is a component of myelin, a protective substance that covers nerves and promotes the efficient transmission of nerve impulses. Before they become part of myelin, newly produced PMP22 proteins are processed and packaged in specialized cell structures called the endoplasmic reticulum and the Golgi apparatus. Completion of these processing and packaging steps is critical for proper myelin development, maintenance, and function.

The extra copy of the *PMP22* gene resulting from the duplication leads to an overproduction of PMP22 protein. Research suggests that excess PMP22 protein may overwhelm cells' ability to process it correctly, leading to a buildup of unprocessed, nonfunctional protein. This buildup may impair the formation of myelin and lead to instability and loss of myelin (demyelination). Shortage and dysfunction of myelin reduce the ability of the peripheral nerves to activate muscles used for movement or to relay information from sensory cells back to the brain, leading to the signs and symptoms of CMT1A.

2.5. Dermatofibrosarcoma protuberans

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 *COL1A1* gene from chromosome 17 with part of the *PDGFB* gene from chromosome 22. 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 researchers believe 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.

2.6. Koolen-de Vries syndrome

Deletion of a small amount of genetic material (a microdeletion) on chromosome 17 can cause Koolen-de Vries syndrome. This disorder is characterized by developmental delay, intellectual disability, a cheerful and sociable disposition, and a variety of physical abnormalities.

Most people with Koolen-de Vries syndrome are missing a sequence of about 500,000 base pairs, also written as 500 kilobases (kb), at position q21.31 on chromosome 17. The exact size of the deletion varies among affected individuals, but it contains at least six genes, including *KANSL1*. This deletion affects one of the two copies of chromosome 17 in each cell.

Because mutations in the *KANSL1* gene cause the same signs and symptoms as the deletion, researchers have concluded that the loss of this gene accounts for the features of Koolen-de Vries syndrome. The protein produced from the *KANSL1* gene is involved in controlling the activity of other genes and plays an important role in the development and function of many parts of the body. Although the loss of this gene impairs normal development and function, its relationship to the specific features of Koolen-de Vries syndrome is unclear.

While Koolen-de Vries syndrome is usually not inherited, most individuals with the condition caused by a deletion have had at least one parent with a common variant of the q21.31 region of chromosome 17 called the H2 lineage. This variant is found in 20 percent of people of European and Middle Eastern descent, although it is rare in other populations. In the H2 lineage, a 900 kb segment of DNA, which includes the region deleted in most cases of Koolen-de Vries syndrome, has undergone an inversion. An inversion involves two breaks in a chromosome; the resulting piece of DNA is reversed and reinserted into the chromosome.

People with the H2 lineage have no health problems related to the inversion. However, genetic material can be lost or duplicated when the inversion is passed to the next generation. Researchers believe that a parental inversion is probably necessary for a child to have the 17q21.31 microdeletion most often associated with Koolen-de Vries syndrome, but other, unknown factors are also thought to play a role. So while the inversion is very common, only an extremely small percentage of parents with the inversion have a child affected by Koolen-de Vries syndrome.

2.7. Miller-Dieker syndrome

Miller-Dieker syndrome is caused by a deletion of genetic material near the end of the short (p) arm of chromosome 17. The signs and symptoms of Miller-Dieker syndrome are related to the loss of multiple genes in this region. The size of the deletion varies among affected individuals. The loss of a particular gene on chromosome 17, called *PAFAH1B1*, is responsible for the syndrome's characteristic sign of lissencephaly, a

problem with brain development in which the surface of the brain is abnormally smooth. This brain abnormality causes severe intellectual disability, developmental delay, seizures, abnormal muscle stiffness (spasticity), weak muscle tone (hypotonia), and feeding difficulties. The loss of another gene, called *YWHAE*, in the same region of chromosome 17 increases the severity of lissencephaly in people with Miller-Dieker syndrome. Additional genes in the deleted region contribute to the varied features of this disorder.

2.8. Potocki-Lupski syndrome

Potocki-Lupski syndrome results from a duplication of a small piece of chromosome 17 in each cell, specifically a region of the short (p) arm designated p11.2. This condition is characterized by delayed development, mild to moderate intellectual disability, behavioral problems including autism spectrum disorder (which affects social interaction and communication), sleep disturbances, and other health problems.

In about two-thirds of affected individuals, the duplicated segment is approximately 3.7 Mb in size. (A missing copy of this segment causes Smith-Magenis syndrome, described below.) In the remaining one-third of cases, the duplication is larger or smaller, ranging from less than 1 Mb to almost 20 Mb. All of these duplications affect one of the two copies of chromosome 17 in each cell.

Although the duplicated region contains multiple genes, researchers believe that having an extra copy of one particular gene, *RAI1*, underlies many of the characteristic features of Potocki-Lupski syndrome. All of the duplications known to cause the condition contain this gene. The *RAI1* gene provides instructions for making a protein that helps regulate the activity (expression) of other genes. Although most of the genes regulated by the RAI1 protein have not been identified, this protein appears to control the expression of several genes involved in daily (circadian) rhythms, such as the sleep-wake cycle. The RAI1 protein also appears to play a role in development of the brain and of bones in the head and face. Studies suggest that the duplication increases the amount of RAI1 protein, which disrupts the expression of genes that influence circadian rhythms. These changes may account for the sleep disturbances that occur with Potocki-Lupski syndrome. Too much RAI1 protein may also disrupt brain development, which could account for delayed development, intellectual disability, behavioral problems, and other neurological features of this condition. Development of the bones in the head and face may also be affected, leading to subtle facial differences in people with Potocki-Lupski syndrome.

2.9. Smith-Magenis syndrome

Smith-Magenis syndrome usually results from a deletion of a small piece of chromosome 17 in each cell, specifically a region of the short (p) arm designated p11.2. This developmental disorder affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems.

Most often, the chromosome segment deleted in Smith-Magenis syndrome is the same one that is duplicated in Potocki-Lupski syndrome (described above). Occasionally the deletion is larger or smaller. All of the deletions affect one of the two copies of chromosome 17 in each cell.

Researchers believe that a loss of function of the *RAI1* gene accounts for many of the signs and symptoms of Smith-Magenis syndrome. All of the deletions known to cause the condition contain this gene. Studies suggest that the deletion leads to a reduced amount of RAI1 protein in cells, which disrupts the expression of genes involved in circadian rhythms. These changes may account for the sleep disturbances that occur with Smith-Magenis syndrome. It is unclear how a loss of one copy of the *RAI1* gene leads to the other physical, mental, and behavioral problems associated with this condition. It is likely that the loss of other genes in the deleted region also influences the signs and symptoms; the role of these genes is under study.

2.10. Yuan-Harel-Lupski syndrome

Duplication of a small piece of chromosome 17 in a region designated p12-11.2 can cause Yuan-Harel-Lupski (YUHAL) syndrome, which is characterized by multiple neurological problems similar to those in Potocki-Lupski syndrome (described above) and CMT1A (described above). In YUHAL syndrome, the duplicated segment ranges in size from about 3 Mb to nearly 20 Mb and always contains the *RAI1* and *PMP22* genes; it may also include additional genes. Certain features of YUHAL syndrome, such as delayed development and behavioral problems, are likely caused by an extra copy of the *RAI1* gene. Other features, including muscle weakness and decreased sensitivity to touch, heat, and cold in the lower legs and feet, are likely due to duplication of the *PMP22* gene.

2.11. Other chromosomal conditions

Other changes in the number or structure of chromosome 17 can have a variety of effects, including intellectual disability, delayed development, characteristic facial features, weak muscle tone (hypotonia), and short stature. These changes include an extra piece of chromosome 17 in each cell (partial trisomy 17), a missing segment of the chromosome in each cell (partial monosomy 17), and a circular structure called a ring chromosome 17. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

2.12. Other cancers

Changes in chromosome 17 have been identified in several additional 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. A particular chromosomal abnormality called an isochromosome 17q occurs frequently in some cancers. This abnormal version of chromosome 17 has two long (q) arms instead of one long arm and one short (p) arm. As a result, the chromosome has an extra copy of some genes and is missing copies of other genes.

An isochromosome 17q is commonly found in a cancer of blood-forming tissue called chronic myeloid leukemia (CML). It also has been identified in certain solid tumors, including a type of brain tumor called a medulloblastoma and tumors of the brain and spinal cord known as primitive neuroectodermal tumors. Although an isochromosome 17q probably plays a role in both the development and progression of these cancers, the specific genetic changes related to cancer growth are unknown.

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