

## 18p-: The Basics

### *Just Diagnosed with 18p-*

Receiving a diagnosis of 18p- can be a very difficult and confusing experience for families. Although it may explain why a child has medical problems or developmental delays, it also brings a lot of new questions. The good news is that we know a lot about 18p-, and we are continuing to learn more through the ongoing research at the Chromosome 18 Clinical Research Center.

We also encourage you to speak with a genetics provider in your area to learn more about what this diagnosis means for you and your family.

### *What is 18p-?*

18p- happens when part of the short arm of one of the two copies of chromosome 18 is missing. This means there is one copy instead of two for each of the genes in the deleted region of the chromosome.

[Learn more about the genetic basis of 18p- on page 4](#)

### *What causes 18p-?*

18p- occurs when a piece of chromosome 18 is lost. This change likely occurred in the egg or sperm prior to conception or very shortly after conception. There is no known cause of 18p-.

### *How is 18p- diagnosed?*

18p- is usually diagnosed when an infant or child has health and/or developmental concerns. Most often, the diagnosis is made by a blood test. This test looks at the chromosomes to see whether a piece of chromosome is missing.

[Learn more about how 18p- is diagnosed on page 6](#)

## *What health problems are associated 18p-?*

18p- can cause several different kinds of birth defects. Heart defects and a certain kind of brain malformation, known as holoprosencephaly, occur in some people with 18p-. They may also have some problems in the newborn period, such as feeding or breathing difficulties. As they get older, they may develop other health problems. For example, people with 18p- are at risk for hormone issues, such as thyroid problems and growth hormone deficiency. Other health concerns may include vision problems, foot problems, and neurological issues, such as seizures or a movement disorder. There are other health problems that have been reported in people with 18p-, but these are the most common.

There is a great deal of variability among people with 18p-. At this point in time, it is impossible to predict exactly how it will affect an individual. However, knowing this diagnosis helps families and their health care team know what to look out for.

Learn more about the health of people with 18p- on page 7

## *Are there any concerns for development in people with 18p-?*

Almost all children with 18p- have developmental delays, usually in the mild range. This means that they may not meet their milestones on time, though they do usually achieve them. For example, they often roll over, walk, and talk later than other children. Nearly all people with 18p- have some intellectual or learning disability. This means they will have more difficulty learning and developing new skills. The degree of intellectual disability varies greatly between different people with 18p-.

## *What do the genes on chromosome 18 do?*

There are 67 genes on chromosome 18p. They play various roles in a person's growth, development, and overall health. Currently, research is focused on understanding how missing specific genes on chromosome 18p lead to health and developmental concerns. We know that many of the genes on 18p do not cause problems when one copy is missing. However, there are a handful of genes that we think may be associated with specific features.

Learn more about genes of interest on 18p on page 11

## *What can I expect for my child with 18p-?*

It is difficult to predict exactly how a person's life will be affected by a deletion of 18p. However, we know that children with 18p- go to school, develop new skills, make friends, and are members of their communities.

## *What should I do for my child with 18p-?*

Every child with 18p- is different. However, we can make some recommendations for evaluations to ensure that the most common concerns are identified and addressed early. The Chromosome 18 Clinical Research Center has created an “[18p- Management Guide](#)”. We strongly recommend reviewing this document with your physician for additional details and information about managing 18p-. Some of the management recommendations include the following:

### Immediate Referrals to:

- Genetics
- Early Intervention

### One Time Evaluations:

- Echocardiogram
- Abdominal ultrasound

### Annual Screenings:

- Thyroid
- Ophthalmology
- Hearing

### Closely Monitor:

- Growth and development
- Allergy symptoms
- Changes in neurological status
- Behavioral & mood concerns

Depending on a person’s health concerns, additional screenings or management strategies may be necessary. It is important to discuss a health care plan with your team of healthcare providers.

## *What research is being done?*

The Chromosome 18 Clinical Research Center is dedicated to fully understanding the chromosome 18 conditions as well as to developing treatments for these conditions. For additional information or to enroll in the study, please visit their [website](#).

## *Where can I go for more support and information?*

[The Chromosome 18 Registry & Research Society](#) is dedicated to making chromosome 18 conditions the first treatable chromosome abnormalities. We count within our membership thousands of parents, siblings, extended family and friends, businesses, and affected individuals. Registry membership is open to any interested person.

We invest in both people and science; supporting our members through education and a sense of community while also focusing squarely on impactful clinical research that will lead to healthier, happier, and more independent lives for those affected and their families.

There is a great deal of additional information on our website, as well as the opportunity to connect with other parents. To become a member, please go to our [home page](#) and click the “become a member” button.

## Genetic Basis of 18p-

As you may already know, 18p- occurs when there is a deletion on the short arm of chromosome 18. You may also be wondering what, precisely, this means.

On this page, we will discuss some basic genetic concepts. However, we also recommend that families meet with a genetics professional, such as a geneticist or a genetic counselor, to talk about the genetic basis of 18p-. A genetics professional will also review the specific genetic change that was identified in the family.

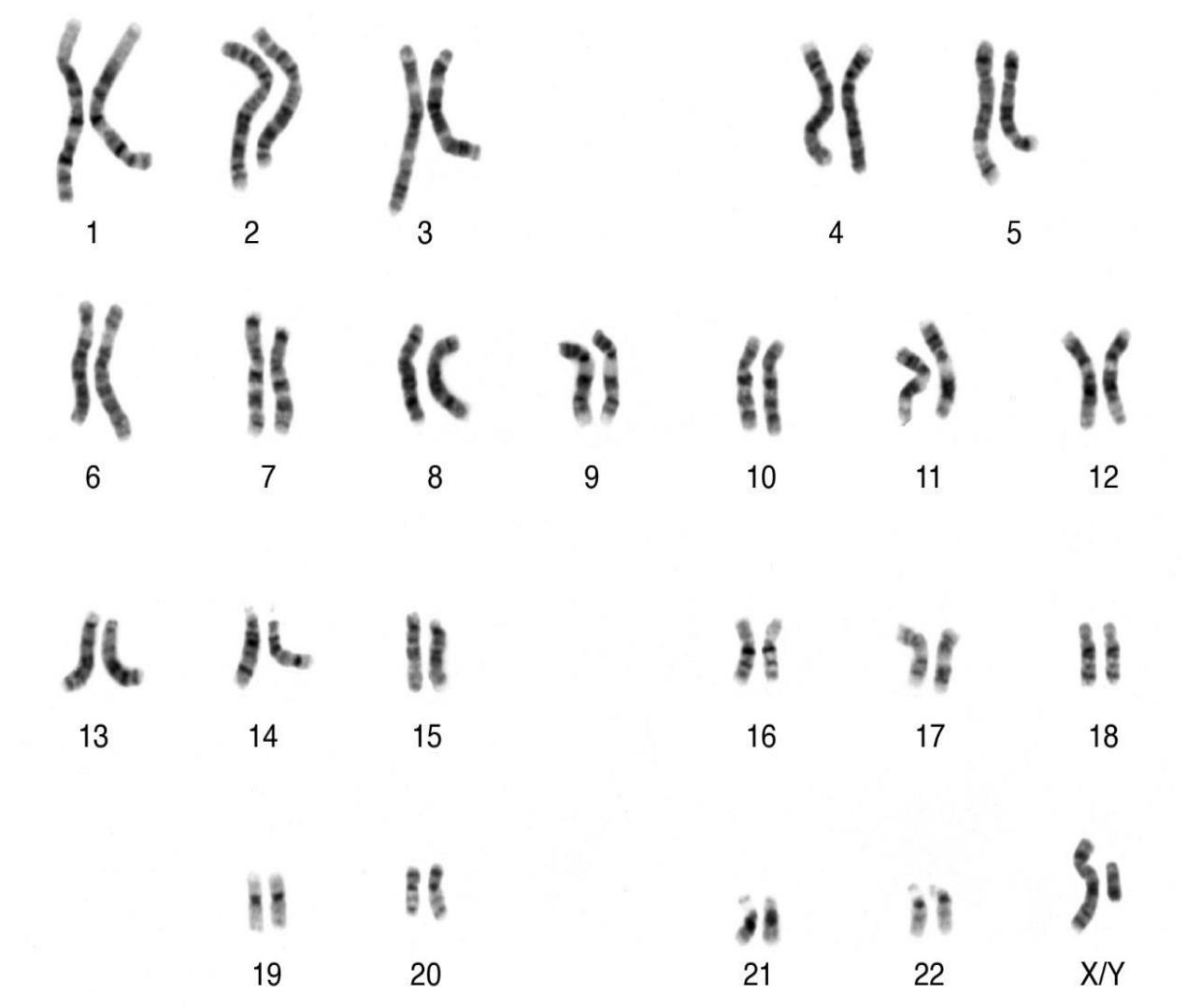
For a more in-depth discussion about genetic concepts, we invite you to review a series of [podcasts](#) designed and narrated by Dr. Jannine Cody, Director of the Chromosome 18 Clinical Research Center.

### *Genes and Chromosomes:*

You have probably heard the word “gene” or “genetic” before, but what is a gene, and how does it relate to health? Put simply, a gene is an instruction. **A gene tells our body how to make a certain protein.** Those proteins, in turn, have many different functions throughout our bodies. Our genes determine many physical features, such as skin, hair, and eye color. Genes also give instructions for proteins that are not so obvious to the naked eye. For example, genes play a role in fetal development, telling the cells and tissues how to form different organs. Genes also continue to play a role after birth, coding for proteins that are involved in day-to-day functions, such as the metabolism of food. **When a gene is changed or is missing, it may affect the protein it is supposed to make, which may, in turn, lead to physical differences or medical and developmental concerns.**

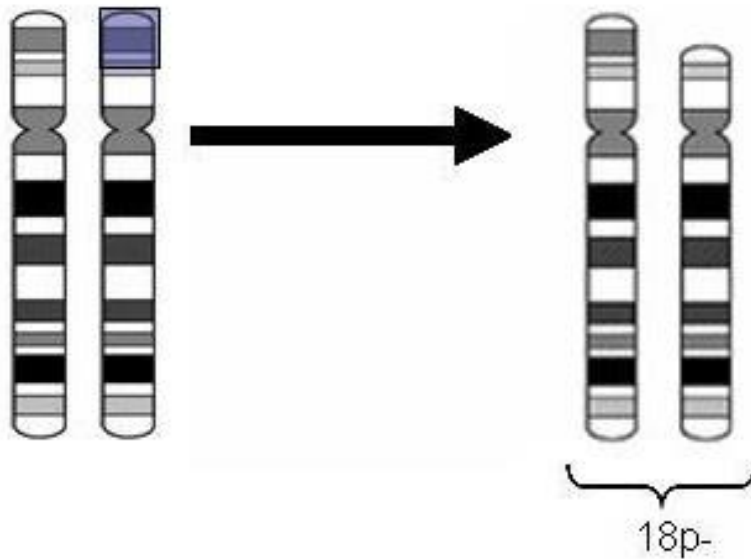
**Genes are located on the chromosomes**, similar to the way that beads may be strung along a necklace. The chromosomes are located in nearly every cell of the body. Each of these cells carries 23 pairs of chromosomes, for a total of 46 chromosomes. We inherit one set of 23 chromosomes from each parent. This means we have two copies of each chromosome, one from our biological mother and one from our biological father. **Because the genes are located on the chromosomes, we typically also have two copies of nearly all of our genes.**

Chromosomes are not visible to the naked eye. However, it is possible to view the chromosomes under a microscope. You can see that each chromosome is unique in its size as well as the striped pattern (known as banding). These differences are noticeable to a trained eye.



In addition to the characteristic banding pattern, chromosomes have different locations of the centromere. The centromere is a tiny constriction somewhere along the length of the chromosome. This constriction divides the chromosome into two different segments. These segments are called arms. The shorter arm (called “p” for petit) is always shown on top. The longer arm is called the “q” arm and is shown below the p arm.

**18p-** occurs when there is a missing piece, known as a deletion, on the p arm of **chromosome 18**. Because the genes are located on the chromosomes, the genes that are located within the deletion are also missing. **In other words, a deletion means that only one copy of the gene is present rather than two.** This is what leads to the health and developmental concerns associated with 18p-.



## Diagnosis of 18p-

There are several different reasons that your family's physicians might suspect that there is an underlying chromosome change present. Some of the more common reasons include:

- Child missing developmental milestones
- Presence of birth defects
- Health problems
- Minor differences in facial features
- A family history of a chromosome condition

Although 18p- can be detected prenatally by chorionic villus sampling (CVS) or amniocentesis, it is most frequently diagnosed during infancy or early childhood. There are two tests that are commonly performed to identify a deletion on 18p. Both of these tests can be performed on a blood sample.

### *Routine Chromosome Analysis*

In this test, white blood cells are grown in the lab. The chromosomes are stained and examined under a microscope by a qualified cytogeneticist. This individual is trained in recognizing extra and missing pieces of chromosomes, as well as other rearrangements, such as translocations and inversions. Results from a chromosome analysis will indicate the number of chromosomes, whether the person is a male or a female, and the general region of the breakpoint of a deletion. The chromosome result of a person with 18p- might look something like this:

**46,XX,del(18)(p11)**

Note that the location of the chromosome break is indicated by the band number in the parentheses to the right. Because each band can include 50 to 100 genes, this is not a very precise way of determining which genes are included in the deletion. For a more precise determination of the breakpoint, molecular analysis is required.

### *Microarray Analysis*

The most common molecular analysis is chromosome microarray analysis. A microarray analysis is similar to a routine chromosome analysis in that it determines if there is extra or missing pieces of a chromosome, but with much greater resolution. It can detect chromosome deletions and duplications that are too small to be visible under a microscope. Because this is a more expensive test, it is often not the first test ordered during a diagnostic workup. However, it is a much more precise test than a routine chromosome analysis. A microarray result includes the molecular breakpoint of the deletion. It can determine with great specificity which genes are included in the deletion. A microarray result of a person with 18p- might look something like this:

**arr 18p11.32p11.21(12,842-15,375,878)x1**

In the example above, the “18p11.32p11.21” tells us the chromosome bands involved. The numbers within the parentheses indicate the base pairs that are involved. The “x1” tells us that only one copy of that section of the chromosome is present. Thus, we know that the deletion extends from about the tip of the chromosome to base pair 15,375,878, which is located at the centromere.

Although microarrays are very useful in determining exactly what is missing and what is extra, they cannot determine some important changes that only affects the arrangement (or rearrangement) of the chromosomes. Microarrays cannot detect chromosome changes that do not involve a gain or a loss of chromosome material. For example, they cannot detect balanced rearrangements, such as balanced translocations or inversions or ring chromosomes. Therefore, we typically suggest that individuals have both a chromosome analysis as well as microarray to fully describe the underlying genetic change.

## 18p-: Health Concerns

This page describes some of the most common health problems that have been reported in people with 18p-. It is important to remember that these concerns do not occur in everyone with 18p-. Also, we do not discuss treatment options or recommendations on this page. It is important that you speak with your team of healthcare providers to make a plan to check for and manage health concerns. In addition, the Chromosome 18 Clinical Research Center has developed [Management Guidelines](#). These documents have more detailed information about the health problems seen in people with 18p-, including how frequently they occur. They also include specific recommendations about checking for health issues.

Lastly, it is important to understand that people with 18p- may develop health problems that are

not listed on this page. As research on the chromosome 18 conditions continues, we will learn more about what to expect for people with 18p- and how to help them stay healthy and live productive, fulfilling lives.

## *Birth Defects*

Babies with 18p- may develop differently in the womb, leading to birth defects. These birth defects may vary from mild to severe.

Heart defects are frequently diagnosed in infants with 18p-. Several different types of heart defects have been reported in infants with 18p-.

Holoprosencephaly is another type of birth defect. In people with holoprosencephaly, the brain does not divide into two separate halves during early fetal development. There is a wide range of severity of holoprosencephaly. In some cases, this condition is severe, and the pregnancy does not survive to delivery, or the baby dies shortly after birth. Other people with holoprosencephaly may have milder forms. For example, an MRI may show that their brain has minor changes, such as a missing corpus callosum (the connection between the two halves of the brain). There may be changes in the facial features as well, such as a cleft lip and or a single incisor (front tooth) located at the midline of the mouth.

Some infants with 18p- have skeletal changes that are apparent at birth. For example, the tailbone of the spine may not develop or develop incorrectly (sacral agenesis or sacral dysgenesis). Some babies have hip dysplasia, which occurs when the thigh bone does not fit properly into the hip socket.

Lastly, hernias have been reported in some newborns with 18p-. A hernia occurs when some organs, often the intestines, push outside of the abdomen into another part of the body. Both inguinal (involving the groin region) and umbilical hernias (involving the umbilical opening) have been seen in babies with 18p-.

## *Problems in the Newborn Period*

Newborns with 18p- often have problems at or shortly after birth. They may have feeding difficulties. For example, they may have problems latching onto the breast or bottle. They may also have problems coordinating the suck-swallow motion that is required to nurse. Some infants may frequently vomit after eating.

Infants with 18p- may also have jaundice. Jaundice is a build-up of bilirubin in the baby's blood, leading to a yellowish color of the skin and eyes.

Some infants with 18p- have breathing problems shortly after birth.



## *Neurological Changes*

People with 18p- have a higher chance of having changes in their nervous and muscular systems. For example, they may have changes in their muscle tone. Many have low muscle tone (hypotonia), though high muscle tone has also been seen. They may have seizures.

Dystonia is another feature of 18p-. The term “dystonia” describes an involuntary contraction of muscles. Because the muscles cannot easily relax, people with dystonia may have twisting, repetitive movements, or changes in their posture. Again, it is important to remember that not everyone with 18p- will develop dystonia.

## *Eyes and Vision*

A minority of people with 18p- are born with cataracts, or a “clouding” of the lens of the eye. As infants with 18p- get older, other vision concerns may become apparent. In particular, strabismus and ptosis are well-known features of 18p-. Strabismus occurs when the movements of the eyes are not coordinated with each other. This is frequently referred to as being “cross-eyed”. Ptosis is the medical term for “drooping eyelids”. In addition, near-sightedness and far-sightedness are fairly common.

## *Hearing*

Children with 18p- have a higher likelihood of having hearing loss. There are two types of hearing loss. Conductive hearing loss describes hearing loss that is caused when there is an obstruction to the transmission of sound from the outer ear to the inner ear. Recurring ear infections are a common cause of conductive hearing loss in people with 18p-.

The second type of hearing loss is called sensorineural hearing loss. This refers to a hearing loss that is caused by a change in the nerves that transmit signals from the ear to the brain.

People with 18p- may have conductive hearing loss, sensorineural hearing loss, or a combination of the two.

## *Gastrointestinal Changes*

Babies and children with 18p- may have some problems with digestion. The most common digestive problem is chronic constipation.

## *Genitourinary Changes*

Males with 18p- have a higher likelihood of having cryptorchidism (undescended testicles). Hypospadias has also been reported in males with 18p-. This occurs when the opening of the urethra is not at the end of the penis.

A minority of people, both male or female, may have kidney abnormalities.

### *Skeletal Changes*

Foot abnormalities are fairly common in people with 18p-. Their feet may be rotated inward or outward. They may also have flat feet.

Other bones in the body may also be affected. People with 18p- may have “bow-leggedness” (genu varum). They may develop scoliosis (an abnormal curvature of the spine) or pectus excavatum (a sunken breastbone).

### *Growth Changes*

Children and adults with 18p- may have changes in their growth patterns. They are often small for their age. In some cases, this is due to growth hormone deficiency. Growth hormone deficiency has been reported frequently within the literature as well as by research participants at the Chromosome 18 Clinical Research Center.

In addition to short stature, many people with 18p- have microcephaly, or a head size that falls below the 3rd percentile.

### *Endocrine Changes*

Some people with 18p- have changes in their hormone levels. These include growth hormone deficiency (discussed above), thyroid problems, diabetes, and others. Individuals with some form of holoprosencephaly, in particular, are at a significant risk for endocrine abnormalities. However, even individuals without holoprosencephaly can develop hormone problems. In some cases, a person with 18p- may have multiple hormone deficiencies. This is called hypopituitarism or panhypopituitarism. These can be very serious conditions that require treatment.

### *Skin*

Some people with 18p- have unique skin differences. Ulerythema ophryogenes describes a rash of small reddish bumps on the faces, particularly in the eyebrow. There is also a high incidence of keratosis pilaris. This term describes small, typically white but sometimes red bumps on the arms, thighs, buttocks, or cheeks. These conditions are mostly a cosmetic concern and don't cause pain or itching.

### *Immunology*

Low levels of IgA are found in some people with 18p-. IgA is a protein that helps fight off

infections. People who have a low level of IgA are more likely to get infections and colds than those with normal levels of IgA.

Recently, we have also learned that people with 18p- seem to have a higher incidence of autoimmune conditions. Autoimmune conditions are a group of disorders that are caused when the immune system mistakenly attacks the body. Lupus, diabetes, and arthritis have all been reported in people with 18p-.

### *Facial Features*

People with 18p- may have facial features that are slightly different from other family members. These changes do not affect a child's health or development. They are simply small differences that might be noted by a doctor.

For example, people with 18p- may have ears that are lower-set and look slightly different from a "typical" ear. They may have an extra fold of skin covering the corner of the eye. The lower jaw may be slightly smaller than that of which is normally seen in people without 18p-.

Although people with 18p- may have facial features in common with one another, it is important to remember that they also have features in common with their family members.

## Genes of Interest on 18p

Here, we will talk about genes on 18p that have been linked to specific health concerns. It is important to have an understanding of basic genetic concepts. You can read about genes and chromosomes [here](#).

Of the 67 genes on 18p, the very large majority do not have an impact when deleted. As of this writing, six genes on 18p have an unknown effect when deleted. There are a handful of genes that we know are associated with significant health concerns. Families and physicians are able to keep track of the latest information about the genes on chromosome 18 through the [Gene Dosage map](#). If you have a concern for one of the conditions described here, it is important to speak with your healthcare provider.

### TGIF1: Holoprosencephaly

This gene is located in chromosome band 18p11.31. About 10% of individuals who are missing TGIF have a particular kind of brain malformation called holoprosencephaly. In people with holoprosencephaly, the brain did not divide into two separate halves during early embryonic development. There is a wide range of severity of holoprosencephaly. In some cases, this condition is severe, and the pregnancy does not survive to delivery, or the baby dies shortly after birth. Other people with holoprosencephaly may have milder forms. For example, an MRI may show that their brain has minor changes, such as a missing corpus callosum (the connection

between the two halves of the brain). There may be changes in the facial features as well, such as a cleft lip and or a single incisor (front tooth) located at the midline of the mouth.

GNAL: Dystonia

This gene can be found in chromosome band 18p11.21. Individuals with deletions that include this gene are more likely to develop a neurologic condition called dystonia. Dystonia is an involuntary contraction of muscles. Because the muscles cannot relax, people with dystonia may have twisting, repetitive movements, or changes in their posture. This condition is most often identified in the teens or early adulthood. At this point in time, we do not know how likely it is that someone missing this gene will develop dystonia. As research advances, we hope to better understand the likelihood of developing dystonia in individuals missing this gene.

SMCHD1: Facioscapulohumeral muscular dystrophy type 2 (FSHD2)

This gene is located in chromosome band 18p11.32. People who are missing one copy of this gene and also have some genetic changes present on chromosome 4 have an increased possibility of having FSHD2. FSHD2 is a type of muscular dystrophy. It causes weakness in several areas of the body, including the face, the shoulders, the upper arms, and the upper legs. However, the grand majority of people with 18p- do not have FSHD, as additional genetic changes are also required to develop features of this condition.

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## Contact Us

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### [A Note Regarding Funding](#)

Chromosome 18 has met the strict criteria for fiscal responsibility set by the Combined Federal Campaign.

### [Combined Federal Campaign & United Way](#)

Federal employees can give through the CFC! The Registry's CFC number is 10291. Texas state employees can also donate through the State Employee Charitable Campaign. Companies participating through the United Way can donate using "Donor's Choice."