THE CHROMOSOME 18
REGISTRY & RESEARCH SOCIETY

Proximal 18q-: The Basics

Just Diagnosed with Proximal 18q-

Receiving a diagnosis of proximal 18q- 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 proximal 18q-, 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 proximal 18q-?

Proximal 18q- happens when a piece of the long 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. This condition is different from another condition called distal 18q-. Proximal 18q- is caused by a deletion that is closer to the center of the chromosome and does not include the tip of the chromosome.

Learn more about the genetics of proximal 18q- on page 4

What causes proximal 18q-?

Proximal 18q- 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 proximal 18q-.

How is proximal 18q- diagnosed?

Proximal 18q- 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 the diagnosis of proximal 18q- on page 6

What problems are associated with proximal 18q-?

Some babies with proximal 18q- may have health problems that are noticeable at birth. For example, they may have a heart murmur or a heart defect. They may also have breathing or feeding difficulties during the neonatal period. Other babies with proximal 18q- may develop health problems as they get older. In particular, people with proximal 18q- have a higher likelihood of having seizures and kidney problems as well as hearing and vision problems. There are other health problems that have been reported in people with proximal 18q-, but these are the most common.

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

Learn more about the health of people with proximal 18q- on page 8

Are there any developmental concerns for people with proximal 18q-?

Most children with proximal 18q- have developmental delays. This means that they do not meet their milestones on time, but they do achieve them. For example, they may roll over, walk, and talk later than other children. Expressive speech may develop later. This means that many children with proximal 18q- are able to understand more than they are able to speak. Almost all people with proximal 18q- will 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.

What do the genes on chromosome 18 do?

There are nearly 300 genes on chromosome 18. 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 18 lead to health and developmental concerns. We know that many of the genes on 18 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 proximal 18q on page 10

What can I expect for my child with proximal 18q-?

It is difficult to predict how an individual will be affected by a deletion of proximal 18q.

However, we know that children with proximal 18q- go to school, develop new skills, make friends, and are active members of their communities.

What should I do for my child with proximal 18q-?

Every child with proximal 18q- 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 a "Proximal 18q- Management Guide". We strongly recommend reviewing this document for additional details and information about managing proximal 18q-. Some of the management recommendations include the following:

Immediate Referrals to:

- Genetics
- Early Intervention

One Time Evaluations:

- Echocardiogram
- Abdominal ultrasound

Annual Screenings:

- Ophthalmology
- Hearing

Closely Monitor:

- Growth and development
- Changes in neurological status

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 Proximal 18q-

As you may already know, proximal 18q- occurs when there is a deletion on the long 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 proximal 18q-. 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.

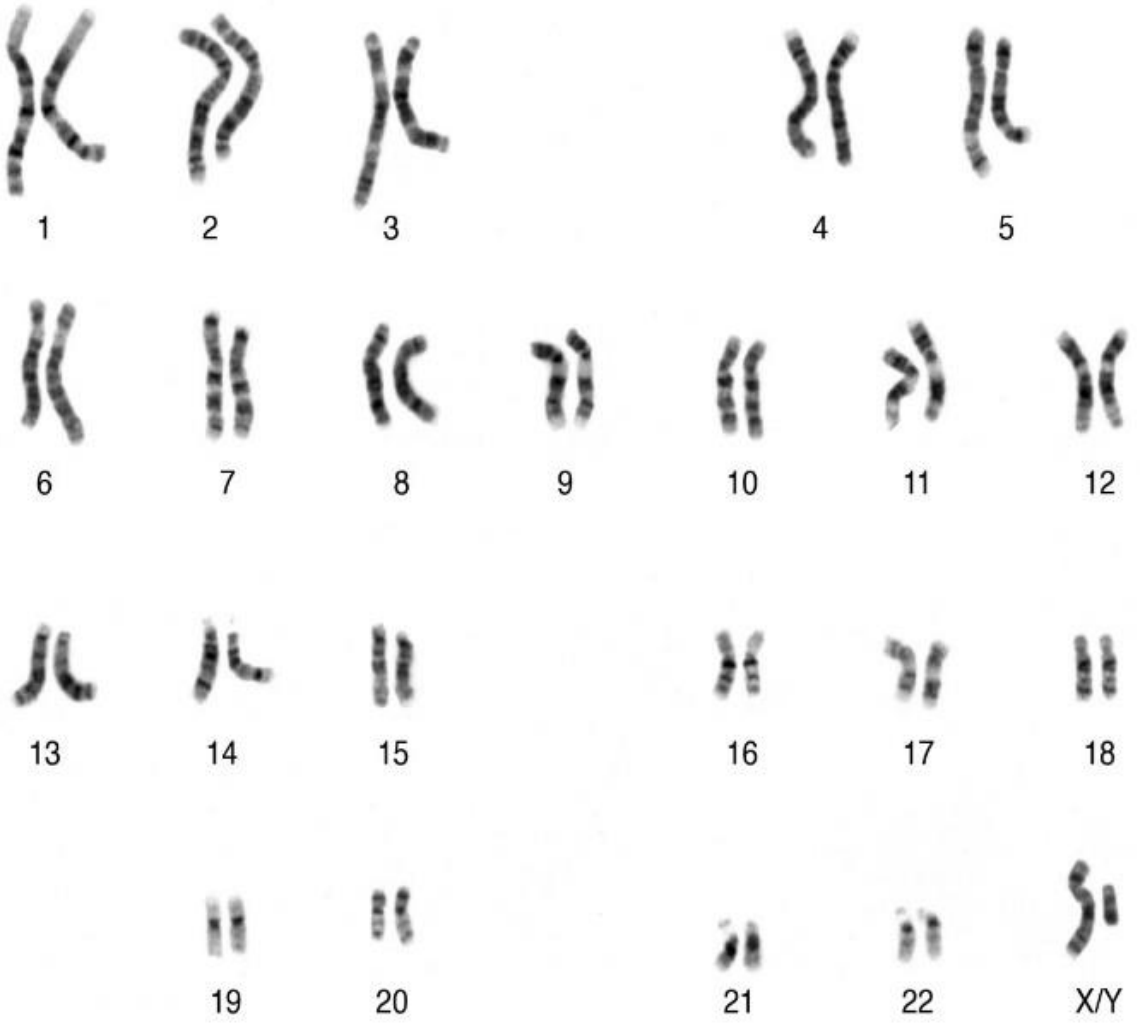
Genes and Chromosomes:

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.



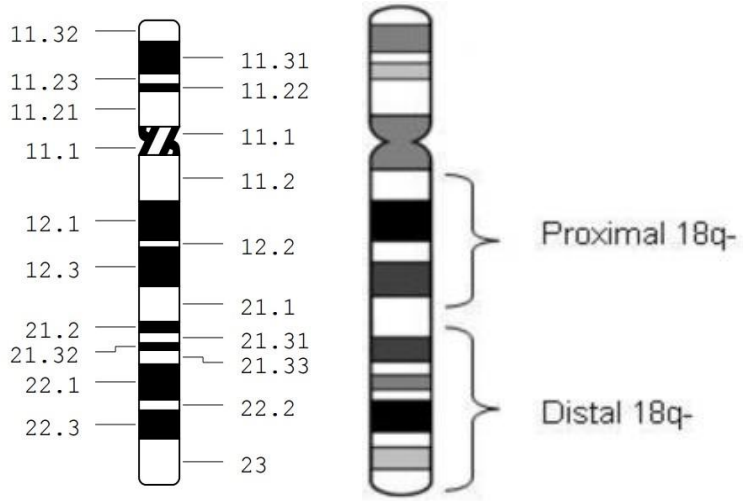
In addition to the characteristic banding pattern, chromosomes have different locations of the centromere. The centromere is a tiny constriction somewhere along the length of the chromosome. This constriction divides the chromosome into two different segments. These segments are called arms. The shorter 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.

Proximal 18q- occurs when there is a missing piece, known as a deletion, on the q 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 proximal 18q-.

Difference between proximal and distal 18q-

Within the Chromosome 18 Registry's website, you will notice that there are two types of 18q-: distal 18q- and proximal 18q-. They may sound similar, but in reality, these are two separate conditions that involve different parts of the long arm of chromosome 18. To understand the difference, it may be helpful to look at a close-up diagram of chromosome 18.

As you can see, the different stripes, or "bands" of the chromosome are labeled with numbers. Proximal deletions involve bands between the centromere and band 21.1. Proximal deletions usually extend from band 12.1 or 12.2 to 21.1. Proximal deletions are all "interstitial". This means that the deletion does not include the tip of the chromosome. In contrast, most distal deletions start at band 21, 22, or 23. These deletions usually include the tip of the chromosome. The diagram below shows which parts of chromosome 18 are involved with these two different types of deletions.



18q-: Diagnosis

There are several different reasons that a healthcare provider might suspect that there is an underlying chromosome change present. Some of the more common reasons include:

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

On rare occasions, 18q- may be detected before a baby is born. However, it is usually diagnosed during infancy or childhood. There are two tests that are commonly performed to identify a

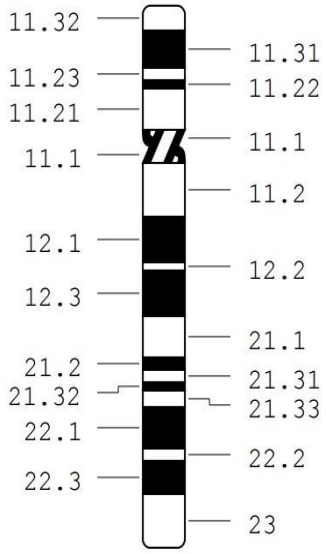
deletion on 18q. Both of these tests are usually performed on a blood sample.

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, missing, and rearranged pieces of chromosomes. Results from a chromosome analysis will tell us the number of chromosomes, whether the person is a male or a female, and which bands of the chromosome are involved in the change. The chromosome result of a person with proximal 18q- might look something like this:

46,XY,del(18)(q21.3)

This result tells us that the person is a male and that they have a deletion on one of their copies of chromosome 18. The "q" tells us that the deletion is located on the short arm of the chromosome. The "21.3" tells us that the deletion begins at band 21.3 and extends to the end of the chromosome. The diagram below shows how the bands of chromosome 18 are labeled.



Each of the bands of a chromosome can include 50-100 genes. Therefore, we cannot tell which genes are involved with the deletion from this test result. For a more precise determination of the breakpoint, a different technology is required.

Microarray Analysis

A microarray analysis is similar to a routine chromosome analysis in that it can tell us if there are extra or missing pieces of a chromosome. However, microarrays can detect chromosome deletions and duplications that are too small to be visible under a microscope. Therefore, it is a

much more precise test than a routine chromosome analysis. A microarray result can tell us with great specificity which genes are included in the deletion.

Although microarrays are very useful in determining exactly what is missing and what is extra, they cannot determine some other types of chromosome changes. Microarrays cannot detect chromosome changes that do not involve extra or missing chromosome material. For example, they cannot detect certain chromosome rearrangements, such as balanced translocations or inversions. Therefore, both tests may be ordered to fully describe the underlying genetic change.

Proximal 18q-: Health Concerns

This page describes some of the most common health problems that have been reported in people with proximal 18q-. It is important to remember that these concerns do not occur in everyone with proximal 18q-. 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 proximal 18q-, including how frequently they occur. They also include specific recommendations about checking for health issues.

Lastly, it is important to understand that people with distal 18q- 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 proximal 18q- and how to help them stay healthy and live productive, fulfilling lives.

Birth Defects

Babies with proximal 18q- may develop differently in the womb, leading to birth defects. Heart defects are the most common. Different types of heart defects have been reported in babies with proximal 18q-.

Problems in the Newborn Period

Newborns with proximal 18q- may 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 vomit frequently after eating.

Infants with proximal 18q- 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.
Lastly, some infants with proximal 18q- have breathing problems shortly after birth.

Neurological Changes

People with proximal 18q- have a higher chance of having changes in their nervous and muscular systems. Many have low muscle tone (hypotonia).

Seizures are a fairly common concern in people with proximal 18q-.

Eyes and Vision

People with proximal 18q- frequently have vision problems. In particular, strabismus and nystagmus can be associated with proximal 18q-. Strabismus occurs when the movements of the eyes are not coordinated with each other. This is frequently referred to as being “cross-eyed”. Nystagmus describes repetitive and uncontrolled movements of the eyes. In addition, near-sightedness and far-sightedness are fairly common.

Hearing

Children with proximal 18q- 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. Recurrent ear infections are a common cause of conductive hearing loss in children with proximal 18q-.

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 proximal 18q- may have conductive hearing loss, sensorineural hearing loss, or a combination of the two.

Gastrointestinal Changes

Babies and children with proximal 18q- may have some problems with digestion. The most common digestive problems include chronic constipation and reflux.

Genitourinary Changes

Some people with proximal 18q- may have kidney problems. Urine may flow backwards from the bladder, sometimes all the way to the kidneys. This is known as vesicoureteral reflux and can damage the kidneys.

Skeletal Changes

Some people with proximal 18q- develop an abnormal curvature of their spine (scoliosis).

Growth Changes

Children and adults with proximal 18q- may have changes in their growth patterns. They are often small for their age. Unlike some of the other chromosome 18 conditions, this growth delay does not appear to be due to growth hormone deficiency.

Facial Features

People with proximal 18q- 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. They may have a prominent forehead, and the middle of their face may look flat. Their eyes may be deep-set.

Although people with proximal 18q- 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 Proximal 18q

Here, we will talk about genes on proximal 18q 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.

At this point, we only know of a few genes on proximal 18q that we know have an effect when one copy is missing. In other words, we cannot link most of the genes on proximal 18q with specific health or developmental concern. As we learn more about the genes on chromosome 18, we will be able to make better predictions about what to expect based on a person's specific deletion. Families and physicians are able to keep track of the latest information about the genes on chromosome 18 through the Gene Dosage map.

Below, we have included information about significant genes on proximal 18q that we know are associated with significant health concerns when deleted.

SETBP1: Expressive Speech Delay and Intellectual Disability

This gene is located in chromosome band 18q12.3. It is believed that this gene is responsible for significant delays in expressive speech. In other words, people who are missing this gene often have discrepancies in what they can understand and what they are able to express through speech. They often are able to understand more than they can verbally indicate. Deletions of this gene may contribute to the intellectual disability that is associated with proximal 18q-.

Of interest, small changes, called point mutations, in *SETBP1* cause a condition called Schinzel-Giedion syndrome. This condition causes significant medical problems, and many babies with this condition do not survive infancy. It is important to note that Schinzel-Giedion syndrome is

not the same condition as proximal 18q-. Although people with proximal 18q- may be missing the *SETBP1* gene, it is not the same kind of genetic change as the one associated with Schinzel-Giedion syndrome.

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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."