Introduction

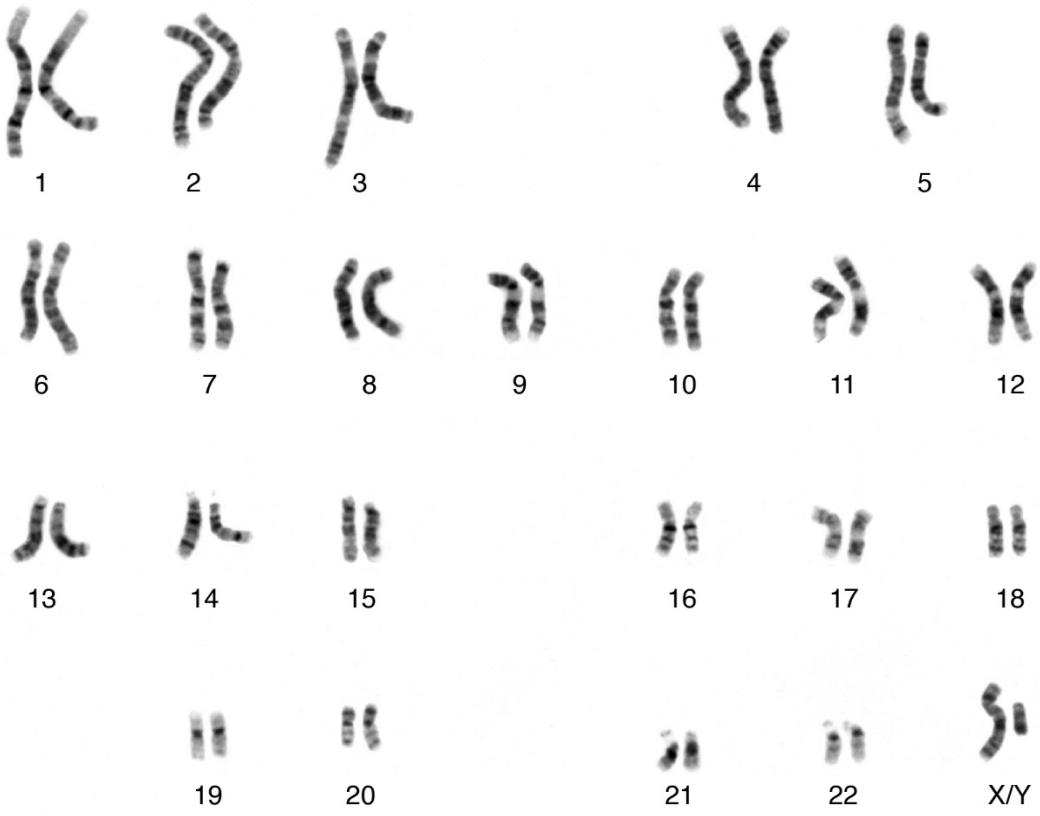
There are two groups of people with 18q deletions: those with deletions within the bottom half of the chromosome (known as distal deletions), and those with deletions closer to the centromere (known as proximal deletions). The goal of this article is to describe the major features of distal deletions of 18q, which we will refer to as "distal 18q-" for the rest of this article. This information was obtained from a thorough review of the literature as well as from the experiences of the Chromosome 18 Clinical Research Center. This information may help you and your healthcare team make decisions about how to care for a person with distal 18q-.

As you read through this article, remember that no two people with distal 18q- are exactly alike. One person may have different medical and developmental concerns from another person with distal 18q-. Also, remember that no one with distal 18q- will have all of the features listed below. In addition, people with distal 18q- share many features with their family members. They will also have their own unique skills and abilities which you will not find in the following list.

Research is critical. As we learn more about distal 18q-, we will also learn more about management and treatment. This will improve the health and development of people with distal 18q-.

Genetic Basis

In order to understand the genetic basis of distal 18q-, it is important to know about the structure of chromosome 18. Every chromosome, including chromosome 18, has a characteristic black and white banding pattern and a constriction (called a centromere) in a characteristic location somewhere along its length. These two things, the banding pattern and the centromere, make each chromosome recognizable under the microscope to a trained eye.



As you can see, the centromere of each chromosome is not exactly in the middle of the chromosome. This makes the chromosome appear as if it has two distinct segments of unequal length. 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. The term “distal” means further from the centromere. And the term “proximal” means closer to the centromere. 18q- describes a missing piece of the long arm of chromosome 18. Thus, “distal 18q-“means that there is a missing piece of the long arm of the chromosome near the end of the chromosome. Often, the tip of the chromosome itself is also deleted.

There are a few different ways we can describe locations along the chromosome. The first way is by chromosome bands. The bands on each chromosome arm divide it up into regions. The regions are numbered starting at the centromere and progressing outward to the end of the chromosome arm. Below is a diagram that shows how the bands of chromosome 18 are labeled.

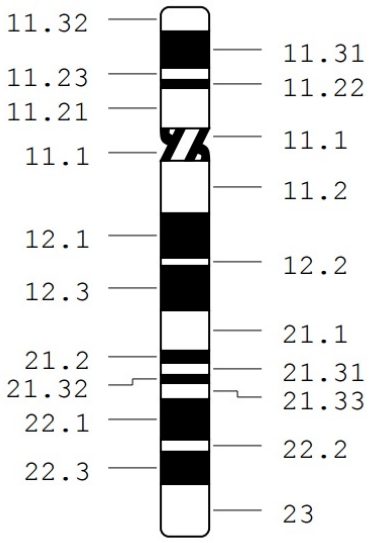


***Image courtesy of the University of Washington (http://www.pathology.washington.edu/research/cytopages/idiograms/human/hum_18.pdf)*

Most distal deletions start at band 21, 22, or 23. These deletions usually go to the end of the chromosome.

We can also describe chromosome locations by their genomic coordinates. A chromosome is actually made up of an organic molecular called DNA. DNA is composed of a long strand of subunits, known as bases. These bases are paired with a complementary base, and together, they form a base pair. We can number the base pairs. The tip of the p arm is base pair 1, and the tip of the q arm is 78,077,248, but we could round it off and say 78 Mb (Megabases).

So far, we have talked about the structure of chromosomes. However, we have not discussed their content. Just as the page numbers of the book are meaningless without the words written on them, chromosomes bands and base pairs are important because they describe the location of the genes. The genes are lined along the chromosome. Genes are the instructions for all the activities necessary for life. They give the body instructions for how to grow and develop. They are the words on the page.

Because we have two copies of each chromosome (one from mom and one from dad), we also have two copies of each gene: one on each chromosome copy. When a piece of a chromosome is deleted, as it is in distal 18q-, the genes in that part of the chromosome are missing as well. For many genes, it does not matter if one of the copies of the gene is missing because there is a copy of the same gene on the non-deleted chromosome.

However, we know that when certain genes are deleted, there can be medical and developmental effects. These are the genes that are linked with the various features of distal 18q-.

In most individuals, the deletion is the only chromosome change present. However, in some cases, the deletion results from a more complicated chromosome rearrangement. For example, some people have distal 18q- because of an unbalanced translocation. An unbalanced translocation may lead to 18q- and a duplication of another piece of chromosome. In this case, predicting what type of problems a child might have is more difficult. People with an unbalanced translocation may have features of distal 18q- as well as features of the chromosome duplication. You can learn more about unbalanced translocations on this page.

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.

Diagnosis

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 delayed in meeting developmental milestones
- Presence of birth defects
- Minor differences in facial features
- A family history of a chromosome condition

Although distal 18q- can be detected prenatally, it is most frequently diagnosed during infancy or early childhood. There are two tests that are commonly performed to identify a deletion on 18q. 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 breakpoint of a deletion. The result of a person with 18q- might look something like this:

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

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, microarray analysis is required.

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 not 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 18q- might look something like this:

arr 18q22.3qter(71,215,307-78,077,000)x1

In the example above, the "18q22.3qter" tells us that the breakpoint begins in the 22.3 band and extends to the end ("*ter*minus") of the q arm. 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 base pair 71,215,307 to the end of the chromosome.

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.

Key Genes

Every unrelated person with a deletion of 18q has a different breakpoint. Therefore, every person's deletion is unique and consequently the exact genes deleted are unique. This is why it is important to have a high resolution diagnosis. Knowing which genes are included in the deletion can give families an idea of what to expect for their child. There are only a few genes on 18q that have an effect when one copy is missing.

Following each of the genes listed below is a long number. These are the genomic coordinates for the gene. These numbers indicate the location of the gene on the chromosome. As time goes on and we learn more about the human genome and its structure, researchers update the information about genomic coordinates. Basically, it is like a draft of a document that is gets updated regularly. The genomic coordinates listed here are from something called the "hg19 build". This phrase refers to the "draft" of the human genome that is being used. The precise genomic locations for the genes below change slightly from draft to draft. If you are comparing the information below to a microarray report, it is important to know which "draft" you are looking at.

SMAD4 (48,556,583-48,611,411): Juvenile Polyposis and Hereditary Hemorrhagic Telangiectasia. We know that people who have mutations in this gene are at risk for two genetic conditions: juvenile polyposis and hereditary hemorrhagic telangiectasia. Juvenile polyposis is a condition that predisposes individuals to developing a certain type of polyp in the gastrointestinal tract. There is an increased risk for cancer associated with these polyps. Hereditary hemorrhagic telangiectasia is a condition that leads to malformations in the way blood vessels are formed. This can cause bleeds in various places of the body, including nosebleeds, the gastrointestinal tract, the brain, the liver, or the lungs.

At this point in time, we don't know precisely what this means for people with distal 18q-. The mutations that have been linked to these conditions are different from the full gene deletions found in people with 18q-. In addition, no individuals within the research study at the Chromosome 18 Clinical Research Center have been diagnosed with these conditions, though none have undergone endoscopies to rule them out, either. That being said, there is one person reported in the literature that has a deletion of 18q as well as JPS. It is reasonable to conclude that there is at least some increased risk for JPS, though the magnitude of that risk is uncertain.

TCF4 (52,889,562-53,303,188): Pitt Hopkins Syndrome. This gene has been linked to a condition first described in 1978 called Pitt-Hopkins syndrome. It is located in chromosome band 18q21.2. If a person with distal 18q- has a deletion that includes *TCF4*, that person is likely to have features of Pitt-Hopkins syndrome as well as the other features of distal 18q-, which are described in detail below.

The features of Pitt-Hopkins include developmental delays, cognitive impairment, breathing abnormalities, and seizures. Read more about Pitt Hopkins Syndrome.*TSHZ1 (72,997,498-73,000,596): Aural Atresia and Stenosis.* This gene was found to be the underlying cause of one of the most common features of distal 18q-: aural atresia and stenosis. It is located in chromosome band 18q22.3. About 80% of people with deletions that include *TSHZ1* have narrow or absent ear canals. This can lead to hearing loss.

There has also been a suggestion that people missing *TSHZ1* are at risk for a particular type of foot anomaly known as congenital vertical talus (CVT), or rocker bottom feet. Cleft palate has also been tentatively linked to deletions of this gene. The palate is the roof of the mouth. Sometimes the palate does not form correctly during development. This results in an opening in the roof of the mouth. A cleft lip occurs when the tissue that forms the upper lip does not fuse during prenatal development. Cleft lip and palate may lead to dental, hearing, speech, and feeding problems. Additional research is necessary to confirm the link between *TSHZ1* and CVT as well as cleft palate.

In addition to the genes listed above, there are a number of genes that are currently under investigation. You can learn about them here.

Critical Regions

In addition to the genes listed above, we have identified several "critical regions". We think that these critical regions contain a gene that causes medical or developmental issues when deleted. However, we have not yet narrowed it down to a single gene. We have only narrowed it down to a small region containing several genes. This information is still helpful, however. If a person's deletion includes a critical region, they may develop that particular finding. Below is a list of recognized critical regions on distal 18q.

Atopic disorders (70,220,470-71,304,427): People that are missing this part of 18q seem to be at an increased risk for allergies. About 60-70% of people with deletions inclusive of this region. Their symptoms may include eczema, hay fever, and allergy-induced asthma.

IgA deficiency (62,548,985-76,923,991): Low levels of IgA are found in about 33-50% of people that are missing this section of chromosome 18. 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. For example, they may have lots of ear and sinus infections.

In most cases, IgA deficiency is managed by treating infections, allergies, and asthma early. There have been some reports of people that require immunoglobulin infusions.

Nystagmus (72,632,502-75,158,616): Nystagmus is an eye condition in which the eyes move involuntarily. About 40% of people who are missing this region of the chromosome have nystagmus.

Congenital heart disease (69,799,020-78,016,181): Heart defects are found in about 25 to 35% of babies with distal 18q-. They may have a hole in the wall separating the chambers of the heart. These types of defects are called "septal defects." There may be changes in the heart valves as well as the major blood vessels that connect to the heart.

Because heart defects are more common in babies with distal 18q-, they may have an ultrasound of the heart (echocardiogram) to look for defects.

Growth Hormone Deficiency (73,540,560-75,158,616): There is a region of 18q that extends from 18q22.3 to 18q23 that has been linked to growth hormone deficiency. Approximately 90% of people who are missing this region will have growth hormone deficiency. This leads to changes growth patterns. If an individual has a growth hormone deficiency, treatment with growth hormone may help normalize growth. It is also possible that treatment may improve a child's development.

If there is a concern regarding growth, a person can see a pediatric endocrinologist to rule out growth hormone deficiency. Drs. Jannine Cody and Daniel Hale have written an article for the Chromosome 18 Registry & Research Society about growth hormone deficiency in children with chromosome 18 abnormalities.

Kidney Abnormalities (73107903-75158616): The region from 18q22.3 to 18q23 has been linked with other medical concerns as well. About 25% of people missing this particular region of the chromosome have some kind of kidney malformation. Several different kinds of kidney abnormalities have been reported and include horseshoe kidney, hydronephrosis, polycystic kidney, and a hypoplastic kidney. We therefore suggest that people who are missing this region or who have a breakpoint within this region have a kidney ultrasound to rule out kidney abnormalities.

Delayed Myelination (72,980,819-75,485,284): Changes in the amount of myelin in the central nervous system have been seen on MRIs of people missing the region from 18q22.3 to 18q23. Myelin is a substance that covers nerve cells much the way the plastic coating covers the wire in an electric cord. The myelin helps transmit electrical signals to and from the brain. It appears that many people with distal 18q- have less myelin. At this point in time, we do not know if or how these changes in the amount of myelin affect a child's development, though we suspect that it slows an individual's processing time. For example, it might take a person with distal 18q- longer to understand an instruction or to respond to a question.

Mood Disorders (72,854,624-73,497,405): We have recently learned that people missing a region in 18q22.3 have an increased risk for psychiatric conditions, such as depression, anxiety, and in a couple of individuals, bipolar disorder. These conditions typically appear during adolescence.

As a child with distal 18q- ages, it is important to screen for mood disorders and to refer to a psychiatrist if concern for such a diagnosis arises.

Cleft palate (72,379,769-76,526,497): People who are missing this region are at an increased risk for clefts, specifically, cleft lips and palates. The palate is the roof of the mouth. Sometimes the palate does not form correctly during development. This results in an opening in the roof of the mouth. A cleft lip occurs when the tissue that forms the upper lip does not fuse during prenatal development. Cleft lip and palate may lead to dental, hearing, speech, and feeding problems. In addition, bifid uvulas are more common in people with 18q-. A bifid uvula occurs when there is a notch in the fleshy structure at the back of the throat. *TSHZ1*, the gene that was discussed above, falls into this critical region. However, there are some other genes that may potentially contribute to clefting in this critical region.

Additional Findings

In addition to the findings discussed above, there are other things that have been reported in people with distal 18q- that have not yet been linked to specific genes or regions on 18q.

Neurological Changes

People with 18q-, particularly infants, may have low muscle tone (hypotonia), poor reflexes, or tremors. About 10% of people with distal 18q- have seizures.

If a person has neurological problems, they may see a neurologist. If seizures are suspected, a doctor may request an electroencephalogram (EEG).

Eyes and Vision

Vision problems are common. The eyes may be misaligned (strabismus) or move involuntarily (nystagmus). Changes in the optic nerve (the nerve that carries signals from the eye to the brain) have also been seen in individuals with distal 18q-. Small gaps in one of the structures of the eye (coloboma) have been reported in a small minority of individuals. Lastly, near-sightedness has been reported in a handful of individuals.

Because vision problems are possible, people with distal 18q- should have regular eye exams.

Ear and Sinus Infections

Babies, toddlers, and children with distal 18q- may have more ear infections than other children. They often have small differences in the structure of the midface (the area between the forehead and the lower jaw). This can lead to poor fluid drainage from the middle ears. A build-up of fluid in the ear can lead to ear infections. In turn, this may lead to hearing problems. Therefore, it is important to identify and treat ear infections. Most of the time, medicine is prescribed to treat the ear infection. Some children may require surgery to insert tubes in the ears to reduce the number of ear infections.

It may be difficult for doctors to diagnose an ear infection in children with distal 18q-. This is because they often have very narrow ear canals (stenosis), or ear canals that end before reaching the ear drum (atresia). In children with these types of changes, the doctor cannot see the eardrum. If a child has symptoms of an ear infection, but the doctor cannot see the ear drum, the doctor may assume that the child has an ear infection and prescribe an appropriate treatment.

Children with 18q- also have more sinus infections than the average child. Sinus and ear infections may have similar symptoms, such as a fever or fussiness. However, the two infections are treated differently. It is important that doctors know that children with distal 18q- can have frequent sinus infections. This will help them to make a correct diagnosis and to treat the child appropriately.

Hearing

As discussed above, hearing loss is fairly common in people with distal 18q-. The degree of loss varies from mild to severe.

Some people have hearing loss because their ear canals are narrow or end before they reach the ear drum, as discussed above. Cleft palates may also contribute to hearing loss. Other people have changes in the nerve that moves sound from the inner ear to the brain. As mentioned above, ear infections may also cause hearing loss.

Recently, we have also learned that people with distal 18q- may have a high frequency hearing loss, similar to the hearing loss that is associated with aging.

Because there are several things that can cause hearing loss in people with distal 18q-, they should have regular hearing screening. This will help find and treat hearing loss early.

Gastrointestinal Changes

Infants and toddlers with distal 18q- often have problems with reflux. This occurs when the stomach contents flow upwards. This can cause pain, irritability, and vomiting. Medication may be as well. In more severe cases, surgery may be required.

Hernias may also occur in babies with distal 18q-. A hernia occurs when some organs, often the intestines, push outside of the abdomen. This problem is usually corrected by surgery.

Genitourinary Changes

Males with distal 18q- may have some changes in the genital region. The testicles may not be fully descended (cryptorchidism). The opening of the urethra may not be at the end of the penis (hypospadias). The penis may turn downward (chordee). In some cases, surgery may be required to correct these concerns.

Changes in the kidneys occur in a small number of males and females with distal 18q-. Some people have vesicoureteral reflux. This occurs when urine flows from the bladder up towards the kidneys. This can lead to recurrent urinary tract infections.

A doctor may order an abdominal ultrasound to rule out structural changes in the kidney. A test called a voiding cystourethrogram may be ordered to examine the flow of urine in the urinary tract.

Orthopedic Changes

Foot abnormalities are fairly common in people with distal 18q-. They may be born with a clubfoot or "rocker bottom" feet. They may also have flat feet or high arches and overlapping toes.

People with distal 18q- may have "bow-leggedness" (genu varum). They may also develop scoliosis or curvature of their spine. All of these bone problems can affect the way they walk and may lead to gait abnormalities.

People with foot, knee, or spinal changes may see an orthopedic specialist. Braces and inserts, surgery, and therapy may help in addressing orthopedic concerns.

Growth

Children and adults may have changes in their growth patterns. Children with distal 18q- are often small for their age. In some cases, this is due to growth hormone deficiency. Treatment with growth hormone helps normalize growth and may improve a child's development.

If there is a concern regarding growth, a person can see a pediatric endocrinologist to rule out growth hormone deficiency. Drs. Jannine Cody and Daniel Hale have written an article for the Chromosome 18 Registry & Research Society about growth hormone deficiency in children with chromosome 18 abnormalities.

The team from the Chromosome 18 Clinical Research Center has also published several manuscripts on this topic in scientific journals.

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

Thyroid Changes

Some people with distal 18q- have thyroid problems. Thyroid hormones regulate a number of functions in the body, including how fast the heart beats and how quickly a person burns calories. Some signs of low thyroid hormone include fatigue, weight gain, and depression.

People with distal 18q- should be screened for thyroid problems once a year. This is because thyroid problems can arise at any time in their life. This screening can be done through an annual blood test. If a thyroid problem is found, an endocrinologist may prescribe medications to treat the problem.

Facial Features

People with distal 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.

The middle of their face may look flat. Their eye openings may be short or slant upwards or downwards. They may have an extra fold of skin covering the corner of the eye. Their ears might be lower and look slightly different than a "typical" ear.

Although people with distal 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.

Lifespan

When a child is diagnosed with distal 18q-, one of the family's first questions is often, "What does this mean for my child's lifespan?" The Chromosome 18 Clinical Research Center has published data regarding life expectancy in people with distal 18q-. Individuals that are missing the *TCF4* gene are at a higher risk for early death. Individuals missing this gene are typically significantly more complicated from both a medical and a developmental standpoint that those who are not missing the *TCF4* gene. They often have problems with breathing, which can lead to aspiration and related complications such as pneumonia. Of the 36 people with distal 18q deletions including the *TCF4* gene, nine (25%) have died between 22 months and 31 years 8 months. In the 235 people with distal 18q- that do not have *TCF4* deletions, there have been four (1.7%) that passed away. The causes for these deaths are not precisely clear. Little information is available for three of those deaths, while the fourth resulted from a persistent epilectic event (seizure activity).

People with 18q- as well as other chromosome changes are also at an increased risk for life-threatening problems. There are 25 individuals with 18q- and another chromosome change enrolled in the study. Five of these have passed away. This is primarily because having additional chromosome imbalances frequently causes additional medical problems.

Development and Behavior:

Individuals with distal 18q- frequently have developmental and behavioral concerns in addition to the medical issues discuss above. The degree of impairment depends greatly on whether or not the deletion includes *TCF4*, the gene linked with Pitt-Hopkins syndrome. Learn more about the affects of the TCF4 gene.

Recommendations for Screenings and Referrals

Based on our current understanding of distal 18q-, there are several evaluations that we would suggest families consider for anyone recently diagnosed with distal 18q-. It is important to work with your team of physicians to determine which of these evaluations are appropriate.

- Genetics evaluation and counseling
- Parental chromosomes
- Periodic ophthalmology evaluations
- Periodic hearing evaluations with consideration of hearing aids, if necessary
- Thyroid testing on annual basis
- Close monitoring of growth and referral to endocrinology if concern about growth presents
- Renal ultrasound to rule out a kidney defect
- Cardiology evaluation to rule out a heart defect
- Orthopedic evaluation for management of foot abnormalities
- Neurology if concerns for seizures are present
- Referral for developmental services and therapy
- Consideration of a communication device if the individual is non-verbal
- Screen for psychiatric and mood disorders and referral to a psychiatrist if concern arises

Family Planning and Genetic Counseling

Many parents wonder, "If we have another child, what is the chance that our next child will have distal 18q-?"

The answer to this question depends on whether a chromosome change has been identified in one of the parents. In 94% of cases, neither parent has a chromosome change. In this situation, the chance that a couple will have another child with distal 18q- is low.

In a small number of families, one parent has an 18q deletion. If a parent has a deletion, there is a 50% chance that they will have a child with distal 18q-.

In some families, the deletion of 18q results from a more complicated chromosome rearrangement in a parent, such as a translocation. In this situation, the likelihood that another child would have a chromosome change depends on what type of rearrangement the parent has and which chromosomes are involved.

If you have questions about the implications of a chromosome change for other family members, we recommend contacting a genetics provider.

For Additional Information

The information provided here is general information based on the literature as well as the experiences in the Chromosome 18 Clinical Research Center. However, every person with distal 18q- is different. Therefore, this information should not replace professional medical advice, diagnosis, or treatment. If you have questions or concerns, you may find it helpful to talk with a clinical geneticist or genetic counselor. You can locate a genetics provider at one of these sites:

Gene Clinics (https://www.genetests.org/clinics/)

NSGC (www.nsgc.org)

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