Introduction

The goal of this article is to describe the major features of deletions of 18p, which we will refer to as “18p−” for the rest of this article. This information was obtained from a thorough review of the literature as well as from the data 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 18p−.

As you read through this article, remember that no two people with 18p− are exactly alike, even if they have the same size deletion. One person may have different medical and developmental concerns from another person with 18p−. Also, remember that no one with 18p− will have all of the features listed below. In addition, people with 18p− 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 18p−, we will also learn more about management and treatment. This will improve the health and development of people with 18p−.

Genetic Basis

In order to understand the genetic basis of 18p−, 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 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 had 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.

18p− occurs when there is a deletion on the short arm of chromosome 18. About half of the deletions of 18p involve the entire arm. The remaining half of individuals have breakpoints that are scattered along the arm of the chromosome.

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.

We can also describe chromosome locations by their molecular 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 meaningful only because they describe the location of the words written on them, chromosome bands and base pairs are important because they describe the location of the genes. The genes are lined along the length of 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 18p−, 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 18p−.
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 18p- because of an unbalanced translocation. An unbalanced translocation may lead to 18p- 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 18p- 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 missing developmental milestones
- Presence of birth defects
- 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:

\[46,XX,\text{del}(18)(\text{p}11)\]

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:

\[\text{arr } 18p11.32p11.21(12,842-15,375,878)x1\]

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 affect 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 and Critical Regions**

In about half of the people with 18p deletions the breakpoint occurs at the centromere. This means that the deletion includes the entire p arm of the chromosome. In the other half of people with 18p deletions, the breakpoints are scattered along the chromosome arm. Each of these individuals has a unique deletion. 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. So far, there are only a few genes on 18p that we know 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 that 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.

**TGIF1**

(3,451,591-3,458,406): 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. Holoprosencephaly is a type of birth defect in which the brain fails to divide into two separate halves during early embryonic development. This term includes a wide range of severity. In some babies, this condition is so severe that they do not survive in the womb or they may die shortly after birth.

Individuals with holoprosencephaly may have a number of different health concerns. Many have developmental delays. Seizures and hydrocephalus (build-up of fluid in the brain) may also occur. Some people with holoprosencephaly may have hormone problems caused by a change in the structure of the pituitary gland in the brain.

**GNAL**

(11,689,014-11,885,683): Dystonia. This gene can be found in chromosome band 18p11.21. Individuals with deletions that include this gene are at risk to develop a certain 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 risk of dystonia in individuals missing this gene.

**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 18p.

**Sensorineural hearing loss (1-1,192,031):** Sensorineural hearing loss (SNHL) refers to a hearing loss caused by changes in the nerves that conduct sound to the brain. In individuals with 18p-, the majority of people who have sensorineural hearing loss have a minimal to moderate hearing loss. About 10% of people who miss this region have SNHL. Because SNHL occurs more frequently in people with 18p-, we recommend that they receive regular hearing screens.

**Strabismus (1-1,192,031):** Strabismus occurs when the movements of the eyes are not coordinated with one another. This is frequently referred to as being “cross-eyed”. About 40% of people missing this region of the chromosome have strabismus. Sometimes, strabismus can be corrected by patching. In other cases, surgery may be necessary.

**Ptosis (1-2,931,532):** Ptosis is a medical term to describe drooping eyelids. This is a common finding in people with 18p-. In one study, about 50% of people missing this region of 18p had ptosis. If the ptosis interferes with vision, surgery may be recommended to lift the eyelids.

**Scoliosis/kyphosis (1-2,931,532):** Abnormal curvature of the spine, known as scoliosis or kyphosis, occurs more frequently in people with 18p-. About 20% of people missing this region of the chromosome has scoliosis or kyphosis. The spine curvature may be present at birth or develop as the child gets older. Some cases of scoliosis or kyphosis are simply monitored, while others require braces or surgery.

**Conductive hearing loss (1-2,931,532):** Conductive hearing loss refers to a hearing loss caused by an obstruction of the mechanical conduction of sound from the outer ear to the inner ear. For example, hearing loss caused by ear infections is a type of hearing loss. Within the population of individuals with 18p-, conductive hearing loss, if present, falls into the minimal to mild range. About 20% of people missing this region of 18p have conductive hearing loss. Because conductive hearing loss occurs more frequently in people with 18p-, we recommend that they receive regular hearing screens.

**Sacral agenesis (1-5,520,172):** Sacral agenesis, also known as caudal regression, is a birth defect in which the bottom part of the spine (the sacrum) does not develop properly. This can lead to various neurologic issues as the spinal cord may be affected. There are varying degrees of severity. Some individuals may use wheelchairs while others are able to walk. Bowel and bladder incontinence are relatively common. About 7% of individuals missing this part of 18p- have sacral agenesis.

**White matter abnormalities (1-5,389,025):** The term “white matter” refers to a part of the central nervous system. It is not uncommon for people with 18p- to have some changes noted in the white matter on MRI. We do not fully understand how these changes affect a person that is missing part of 18p. However, we do know that about 50% of people who are missing this region of the chromosome have white matter abnormalities.

**Cryptorchidism (1-5,520,172):** Cryptorchidism is the medical term for undescended testicles. It means that the testicles have not moved into the scrotum in male infants. This condition is present at birth. About 15% of males that are missing this region have cryptorchidism. In some cases, no intervention is necessary. The testicles descend into the scrotum as the baby gets older. In other cases, surgery may be necessary.

**Tetralogy of Fallot (1-9,148,020):** This is a specific type of heart defect that is actually composed of four different changes in the heart’s anatomy. This condition is treated with surgery. In research published by the Chromosome 18 Clinical Research Center, 7% of people that are missing this critical region have this heart defect.

**Pectus excavatum (1-9,148,020):** Pectus excavatum describes a caved-in, sunken appearance of the chest caused by a change in the way the ribs and sternum grow. In people with 18p-, there is a higher rate of this particular orthopedic abnormality. About 30% of people missing this region of the chromosome have pectus excavatum.

**Pituitary anomalies (1-9,849,184):** The pituitary gland is located in the brain. It is responsible for making several hormones, including ones that play a role in thyroid function, growth, and metabolism, among others. Some people that
are missing this region of 18p have some structural pituitary abnormalities, including absence of the entire or a part of the pituitary or the undergrowth of the pituitary. About 15% of people who are missing this part of the chromosome have some pituitary anomalies. In addition, even individuals with normal appearing MRI’s may have hormone problems. Because thyroid abnormalities can occur as a result of pituitary problems, we suggest that people with 18p- have annual thyroid screens. We also recommend that people with 18p- have their growth closely monitored. If there is a concern about growth, we recommend referral to an endocrinologist to evaluate for growth hormone deficiency.

Seizures (1-10,952,107): About 10% of people with 18p- have seizures. There does not appear to be one specific type of seizure associated with 18p-. In the research study group, there are some with grand mal, some with absence, and another with partial complex seizures. The average age at seizure onset was 11 years old. These are most commonly managed with medication.

Autoimmune disorders (1-12,317,830): Rheumatoid arthritis has long been reported in association with 18p-. In recent years, however, researchers have started to recognize that people with 18p- are at risk for other types of autoimmune conditions as well. For example, we’ve had several people in the research study that have been diagnosed with alopecia, vitiligo, and Graves’ disease, among other autoimmune diagnoses. About 20% of people who are missing this region of the chromosome have autoimmune conditions.

Hip dysplasia (1-13,325,333): Congenital hip dysplasia occurs when there is a misalignment of the hip joint. It is not a very common feature of 18p-; about 4% of people missing this section of the chromosome have hip dysplasia. Hip dysplasia can be treated with a harness or cast or, in some cases, surgery.

Congenital cataracts (1-13,325,333): Congenital cataracts are opacities of the lens of the eye. Basically, the eye is cloudy. About 7% of people missing this region of the chromosome have congenital cataracts. This condition is easily treatable with surgery.

Additional Characteristics of 18p-

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

Problems in the Newborn Period

Newborns with 18p- often have problems at birth or shortly thereafter. For example, they may be nursing/feeding difficulties. Infants 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. In some cases, a referral to an occupational or physical therapist may be recommended. In more serious cases, a feeding tube may be required. Supplementing their diet with a high-calorie formula may also be recommended to help the infant gain weight.

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. Occasionally, this resolves on its own. However, many infants with 18p- require treatment for jaundice. Treatment is usually very easy. Typically, the baby is simply placed under a light. This helps break down the extra bilirubin in the baby’s blood.

Some infants with 18p- have breathing problems shortly after birth. To assist with the baby’s breathing, doctors may have to provide extra oxygen. This may be done by putting a tube into the baby’s nose.

Neurological Changes

There are a few neurologic concerns that occur more frequently in people with 18p-, such as holoprosencephaly sacral agenesis, and seizures, all of which have been linked to specific regions on 18p. In addition to these findings, they may have low muscle tone (hypotonia).
If there are neurological concerns, a person may be referred to a neurologist for a complete evaluation. If there is a concern of seizures, a primary care physician or a neurologist may request an electroencephalogram (EEG). If a person with 18p- has sacral agenesis and the associated neurologic problems, neurosurgery to release the spinal cord may be recommended.

**Eyes and Vision**

Vision problems are often found in people with 18p-. In particular, strabismus and ptosis are well-known features of 18p-, as reviewed above. In addition, near-sightedness and far-sightedness are fairly common.

Because vision problems are possible, people with 18p- should have regular eye exams. In some cases, surgery may be required to treat strabismus or ptosis.

**Ear Infections**

As mentioned above, many children with 18p- are at risk for both conductive and sensorineural hearing loss. In some cases, the conductive hearing loss may be caused by recurrent ear infections. Ear infections may lead to hearing problems if left untreated. 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.

Because there is a risk for hearing loss due to the ear infections, people with 18p- should have regular hearing screening. This will help find and treat hearing loss early.

**Heart**

Heart defects are found in about 25% of babies with 18p-. As mentioned above, tetralogy of Fallot in particular has been linked to a specific region on 18p. However, there are other types of heart defects that have been reported in babies with 18p- as well. There doesn’t appear to be a specific type of heart defect that is more commonly associated with 18p-.

Because heart defects are more common in babies with ring 18 than in those without ring 18, an echocardiogram (ultrasound of the heart) may be recommended to look for defects.

**Gastrointestinal and Other Abdominal Changes**

Babies and children with 18p- may have some problems with digestion. The most common digestive problem is chronic constipation. A physician may prescribe dietary changes or medication to help manage constipation.

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

There have been a very limited number of reports in the scientific literature of people with 18p- and a rearrangement of their internal organs or additional organs. For example, in one individual, the location of the internal organs was reversed (situs inversus). In other individuals, there was an extra spleen (accessory spleen), or a malrotation of the intestines. In these case reports, the changes did not require surgical correction. It should be noted, however, that these types of malformations may require surgical intervention on occasion.
**Genitourinary Changes**

As mentioned above, males are at risk for cryptorchidism (undescended testicles) if they are missing the critical region. 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 (hypospadias). In some cases, surgery may be required to correct these concerns.

**Musculoskeletal Changes**

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

People with 18p- may have “bow-leggedness” (genu varum). They also have a higher risk of certain spinal malformations. Sacral agenesis, or a failure of the development of the bottom of the spine, has been reported in a number of individuals. People with 18p- may also develop an abnormal curvature of their spine (scoliosis).

People with foot, knee, or spinal changes may be referred to an orthopedic specialist by their regular medical doctor. 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 18p- 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.

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 18p-.

- **Growth Hormone Deficiency and Chromosome 18 Abnormalities, Chromosome 18 Communiqué, Spring 1999**

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

**Endocrine**

Some people with 18p- have changes in their pituitary hormone levels. These include growth hormone (discussed above), thyroid stimulating hormone, and others. Individuals with some form of holoprosencephaly are at a significant risk for endocrine abnormalities. However, even individuals without holoprosencephaly can develop hormone irregularities. In some cases, a person with 18p- may have multiple hormone deficiencies. This is called hypopituitarism or panhypopituitarism.

People with 18p- should be screened for thyroid problems once a year. In addition, if there are any concerns for other kinds of endocrine abnormalities, a referral should be made to an endocrinologist.

**Skin**

A specific kind of skin change has been reported in numerous individuals with 18p-. Ulerythema ophryogenes describes a rash of small reddish bumps on the face, particularly in the eyebrows. There is also a high incidence of keratosis pilaris, which 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. However, if these cosmetic concerns are interfering with daily life, there are some treatment options. A dermatologist can complete a physical exam and make recommendations for treatments.
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 that those with normal levels of IgA. 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.

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 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.

Lifespan

When a child is diagnosed with 18p-, 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 18p-, as well as other chromosome 18 conditions. There are 91 individuals included in this paper. One passed away following complications during cardiac surgery. There has also been another young adult who passed away from complications arising from lupus.

Development and Behavior:

Individuals with 18p- frequently have developmental and behavioral concerns in addition to the medical issues discussed above.

Recommendations for Screenings and Referrals

Based on our current understanding of distal 18p-, 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; consideration of surgery if ptosis is causing impaired vision
- Periodic audiology evaluation
- ENT referral for management of chronic otitis media
- Cardiology evaluation
- Annual thyroid testing
- Endocrine evaluation if concerns for pituitary dysfunction present
- Neurology evaluation if concerns for dystonia or seizures present
- Dermatology evaluation if skin problems cause discomfort or cosmetic problems
- Referral for developmental services and therapy
Family Planning and Genetic Counseling

Many parents wonder, “If we have another child, what is the chance that our next child will have 18p-?”

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

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

In some families, the deletion of 18p 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 of the Chromosome 18 Clinical Research Center. However, every person with 18p- 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:

GeneTests Clinic Directory

National Society of Genetic Counselors