THE CHROMOSOME 18
REGISTRY & RESEARCH SOCIETY

Tetrasomy 18p-: The Basics

Just Diagnosed with Tetrasomy 18p

Receiving a diagnosis of Tetrasomy 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 Tetrasomy 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 Tetrasomy 18p?

Tetrasomy 18p occurs when there is an extra chromosome that is made up of two copies of the short arm of chromosome 18 (the p arm). Instead of having two copies of the p arm of chromosome 18, people with Tetrasomy 18p have four copies.

Learn more about the genetic basis for Tetrasomy 18p on page 4

What causes Tetrasomy 18p?

Tetrasomy 18p occurs when there is an extra chromosome made of material from the short arm of chromosome 18. This change likely occurred in the egg or sperm prior to conception or very shortly after conception. There is no known cause of Tetrasomy 18p.

How is Tetrasomy 18p diagnosed?

Tetrasomy 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 chromosome to see whether there are any extra or missing pieces of chromosome.

Learn more about how Tetrasomy 18p is diagnosed on page 6

What problems are associated Tetrasomy 18p?

Some babies with Tetrasomy 18p may have health problems that are noticeable at birth. For example, they may have a heart defect or spina bifida. Spina bifida occurs when the spine does not close during fetal development, leaving some of the spinal cord exposed. Other birth defects have been seen in babies with Tetrasomy 18p, including hernias and foot abnormalities. Newborns with Tetrasomy 18p may have breathing or feeding difficulties during the neonatal period. Other health problems may occur as a person with Tetrasomy 18p gets older. People with Tetrasomy 18p 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 Tetrasomy 18p, but these are some of the most common.

There is a great deal of variability among people with Tetrasomy 18p. At this point in time, it is impossible to predict exactly how it will affect an individual, 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 Tetrasomy 18p on page 7

Are there any developmental concerns for Tetrasomy 18p?

Most children with Tetrasomy 18p have developmental delays. This means that they do not meet their milestones on time. For example, they may roll over, walk, and talk later than other children. People with Tetrasomy 18p have intellectual 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. At this point in time, we do not know which genes on 18p are responsible for the features of tetrasomy 18p.

What can I expect for my child with Tetrasomy 18p?

It is difficult to predict how an individual will be affected by Tetrasomy 18p. However, we know that children with Tetrasomy 18p go to school, develop new skills, make friends, and are active members of their communities. As adults, some individuals with Tetrasomy 18p have part time employment but all live in a supervised environment.

What should I do for my child with Tetrasomy 18p?

Every child with Tetrasomy 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 a "Tetrasomy 18p Management Guide". We strongly recommend reviewing this document with your physician for additional details and information about managing Tetrasomy 18p. 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
- Allergy/autoimmune symptoms
- 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 Tetrasomy 18p

As you may already know, Tetrasomy 18p occurs when there is an extra chromosome that is made up of two copies of 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 Tetrasomy 18p. A genetics professional will also review the specific genetic change that was identified in the family.

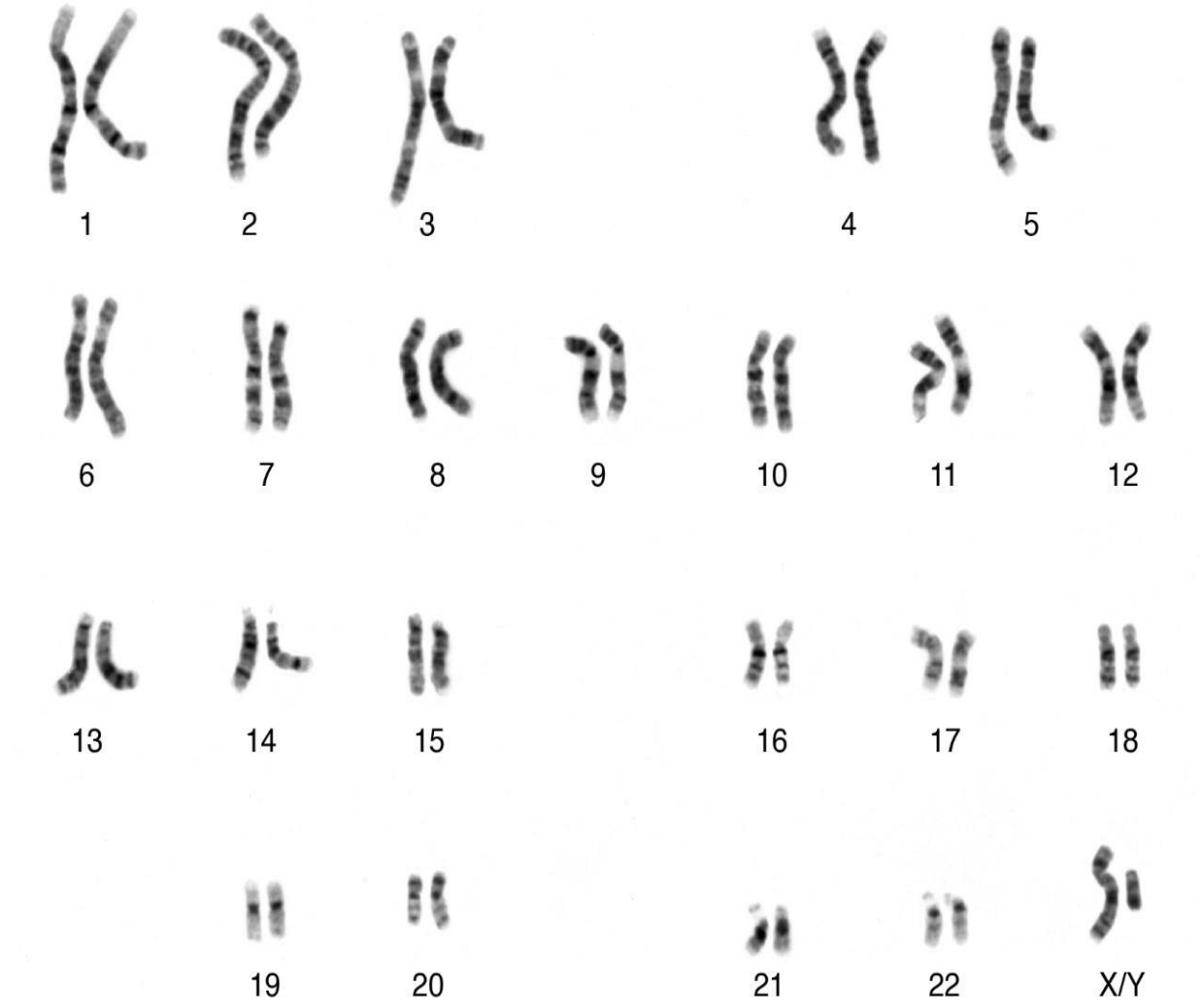
For a more in-depth discussion about genetic concepts, we invite you to review a series of podcasts designed and narrated by Dr. Jannine Cody, Director of the Chromosome 18 Clinical Research Center.

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.

Individuals with Tetrasomy 18p have 47 chromosomes instead of 46. The extra chromosome, also called an "isochromosome" is made up of two additional copies of the short arm of chromosome 18. Therefore, there are a total of four copies of the short arm (p arm) of chromosome 18. This is why the condition is called Tetrasomy 18p. The prefix "tetra" simply means "four". You may also see the term "isochromosome 18p" used to describe this condition.

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

duplicated, the genes in that part of the chromosome are duplicated as well. Because people with Tetrasomy 18p have four copies of 18p, they also have four copies of each of the genes in that region. The change in the number of genes leads to the medical and developmental concerns associated with Tetrasomy 18p.

Diagnosis of Tetrasomy 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
- Birth defects
- Health problems
- Minor differences in facial features
- A family history of a chromosome condition

Although Tetrasomy 18p can be diagnosed 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 Tetrasomy 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 which part of the chromosome is changed. The chromosome result of a person with Tetrasomy 18p might look something like this:

47,XX,+i(18)(p10)

This result tells us that there are 47 chromosomes instead of the expected 46. This person is also a female, as indicated by the two copies of the X chromosome. The "i" stands for isochromosome, which is composed of material from chromosome 18. The "p10" tells us that the isochromosome is made of chromosome material that starts at the centromere (p10) and extends to the tip of p arm.

Microarray Analysis

A microarray analysis is similar to a routine chromosome analysis in that it determines if there are extra or missing pieces of a chromosome. It can detect chromosome deletions and duplications that are not visible under a microscope. A microarray result of a person with Tetrasomy 18p might look something like this:

arr 18pterp11.21(136,226-15,198,990)x4

This result tells us that there is a change in the region extending from the tip of chromosome 18p to base pair 15,198,990, which is essentially the centromere. The "x4" at the end tells us that there are actually four copies of that region, which is consistent with a diagnosis of Tetrasomy 18p.

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.

Tetrasomy 18p: Health Concerns

This page describes some of the most common health problems that have been reported in people with Tetrasomy 18p. It is important to remember that these concerns do not occur in everyone with Tetrasomy 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 Tetrasomy 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 Tetrasomy 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 Tetrasomy 18p and how to help them stay healthy and live productive, fulfilling lives.

Problems in the Newborn Period

Newborns with Tetrasomy 18p often have problems at birth or shortly thereafter. The most common problem is 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 a speech language pathologist 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 Tetrasomy 18p may have other problems. 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 Tetrasomy 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 Tetrasomy 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

People with Tetrasomy 18p usually have some changes in their muscle tone. They may have increased or decreased muscle tone. This is called hypertonia and hypotonia, respectively. Changes in muscle tone can lead to other difficulties. For example, infants with low muscle tone may have difficulty eating because the muscles surrounding the mouth are weak. Children with high muscle tone may also have spasticity. This means that there are uncontrolled muscle spasms when the muscle is stretched by someone else. Changes in muscle tone and spasticity may also lead to delays in meeting developmental milestones, such as sitting without support and walking. Physical, occupational, and speech therapy may improve some of these problems.

Seizures also happen more often in people with Tetrasomy 18p than in people without Tetrasomy 18p. If seizures are suspected, a doctor may request an electroencephalogram (EEG). They may also refer the patient to a neurologist to help manage the seizures.

Spina bifida has been reported in a small number of people with Tetrasomy 18p. Spina bifida, also known as myelomeningocele, is a type of birth defect. It is an opening in the spinal cord that occurs early in the first trimester of pregnancy. This can lead to paralysis of the legs, problems with the kidneys and urinary system, and hydrocephalus (extra fluid in the brain). Spina bifida is usually treated by a team of specialists, including neurosurgeons, therapists, and urologists. To find a spina bifida clinic in your area, visit the Spina Bifida Association website.

MRI Changes

Some people with Tetrasomy 18p have changes in the structure of their brain that can only be detected with an MRI. For example, several people have been identified with a thin corpus callosum. The corpus callosum is the bundle of nerves that connect the right and the left sides of the brain. Other people have been diagnosed with "enlarged lateral ventricles". This simply means that the spaces that contain the cerebrospinal fluid in the brain are larger than expected.

Eyes and Vision

Eye problems are common in people with Tetrasomy 18p. The eyes may be misaligned (strabismus). People with Tetrasomy 18p may also have problems with their vision. They may be near-sighted, far-sighted, or have astigmatism.

Because vision problems are possible, people with Tetrasomy 18p should have regular eye exams.

Ear Infections

Recurrent ear infections are common in babies and toddlers with Tetrasomy 18p. They occur in approximately 50% of individuals. Untreated ear infections 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.

Hearing

Although hearing loss does occur in some people with Tetrasomy 18p, the majority do not have any hearing problems. It appears that those that do have hearing loss typically have a mild to moderate hearing loss.

Although hearing loss is not very common in people with Tetrasomy 18p, it is still important to screen them for any potential hearing problems. This will help find and treat hearing loss early.

Palatal Abnormalities

The palate is the roof of the mouth. Many people with Tetrasomy 18p have changes in the shape of their palate. For example, the palate may be highly arched and/or narrow. In some cases, these changes may lead to some difficulties with speech. It is important to understand that this is not the same thing as a cleft palate, in which the palate does not completely close.

If a physician feels that a change in the palate may lead to speech problems, he or she may refer a patient to an ENT (a doctor who specializes in problems of the ears, nose, and throat).

Heart

Approximately 30% of people with Tetrasomy 18p have some type of heart defect. Many of the heart defects are "septal defects", meaning that there is a hole in between the two sides of the heart. In some cases, these defects close without any intervention. However, in some cases, surgery is necessary.

Because heart defects are more common in babies with Tetrasomy 18p, they may have an ultrasound of the heart (echocardiogram) to rule out such defects.

Gastrointestinal Changes

Gastrointestinal problems are fairly common in people with Tetrasomy 18p. The most common concern is constipation. Reflux also occurs somewhat frequently. Structural malformations of the gastrointestinal system are not very common. However, pyloric stenosis and hernias have been reported. Pyloric stenosis is a closure or narrowing of the place where the stomach contents enter the intestines. A hernia occurs when some organs, often the intestines, push outside of the abdomen.

If there is a concern for gastrointestinal problems, a referral to a gastroenterologist is appropriate.

Genitourinary Changes

Males with Tetrasomy 18p 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). In some cases, surgery may be required to correct these concerns.

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. However, structural changes in the kidneys occur in a small number of males and females with Tetrasomy 18p. A doctor may order an abdominal ultrasound to rule out structural changes in the kidney.

Orthopedic Changes

Some people with Tetrasomy 18p may have minor changes in their hands and feet. For example, they may have narrow feet, or they may have fingers and toes that are partially fused. They may have camptodactyly. Camptodactyly occurs when fingers are in a permanently "flexed" position. However, these issues seldom require medical intervention.

People with Tetrasomy 18p may have scoliosis or kyphosis. This simply means that they have an abnormal curvature of the spine. Flat feet are another common orthopedic concern.

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

There has been some evidence suggesting that people (including children) with Tetrasomy 18p have decreased bone mineral density, meaning that they may be more susceptible to bone fractures. A DEXA scan (bone scan that determines bone mineral density) may be considered to establish a baseline. Families may also wish to speak with their physician about calcium and vitamin D supplementation. Much research remains to be done to understand whether and how bones are affected in individuals with Tetrasomy 18p.

Allergy and Immunology

In recent years, several individuals have been diagnosed with eosinophilic esophagitis (EoE). EoE is an inflammatory disease that affects the tube that connects the mouth to the stomach (the esophagus). Some symptoms include feeding difficulties and failure to thrive, reflux that doesn't respond to therapy, difficulty swallowing, nausea, and vomiting. For more information about EoE, visit the American Partnership for Eosinophilic Disorders.

If there is a concern for EoE, a gastroenterologist can help make a diagnosis and discuss treatment and management options.

Growth

Children and adults may have changes in their growth patterns. Children with Tetrasomy 18p may be small for their age. In a minority of 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.

- Growth Hormone Deficiency and Chromosome 18 Abnormalities, Chromosome 18 Communique, Spring 1999.

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

Bone Issues

There has been some evidence suggesting that people with Tetrasomy 18p have decreased bone mineral density, meaning that they may be more susceptible to bone fractures. A DEXA scan (bone scan that determines bone mineral density) may be considered to establish a baseline. Families may also wish to speak with their physician about calcium and vitamin D supplementation. Much research remains to be done to understand whether and how bones are affected in individuals with Tetrasomy 18p.

Facial Features

People with Tetrasomy 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.

They may have changes in the structure or the placement of the ears. They may have a small mouth, and the area above the upper lip may be smooth. The upper lip may be thin. Their chin may be either larger or smaller than other children's chins.

Although people with Tetrasomy 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 Tetrasomy 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 Tetrasomy 18p. There are 56 individuals with Tetrasomy 18p in the study. In this group, there has been at least one instance of premature death in a person with Tetrasomy 18p. A thirteen year old girl passed away unexpectedly due to sudden heart arrest following a day-long history of nausea, vomiting and lethargy. The direct cause of her sudden deterioration is unknown. She had a history of severe and untreated constipation as well as possible seizures which may have contributed to her death.

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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."