Introduction

The goal of this article is to describe the major features of ring 18. 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 ring 18.

As you read through this article, remember that no two people with ring 18 are exactly alike. One person may have different medical and developmental concerns from another person with ring 18. Also, remember that no one with ring 18 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 ring 18, we will also learn more about management and treatment. This will improve the health and development of people with ring 18.

Genetic Basis

In order to understand the genetic basis of ring 18, 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.

Ring 18 occurs when the tips of the chromosome join together to form a ring-shaped chromosome. During the formation of this ring chromosome, the tips of both the q and the p arms are deleted. However, no two individuals with ring 18 have the same breakpoints. This means that every person with ring 18 has different amounts of the chromosome missing. Some people are missing only a little bit of genetic material while others are missing a considerable amount.

We 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 chemical subunits called nucleotides. We can actually number the nucleotides that make up a chromosome. The tip of the p arm of chromosome 18 is nucleotide 1, and the tip of the q arm is 78,077,248.

So far, we have talked about the structure of chromosomes. However, we have not discussed their content. We can think of the chromosome number as chapters and nucleotide numbers as pages in a book. Just as page numbers can tell us the location of a sentence in a book, the nucleotide position tells us the location of a gene on a chromosome. The genes are the instructions for all the activities necessary for life. They tell the body how to grow and develop. 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 pieces of a chromosome are missing, as is the case in individuals with ring 18, 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.

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 ring 18 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 18p. Both of these tests can be performed on a blood sample.

Routine Chromosome Analysis

In this test, the chromosomes from a person's white blood cells 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 breakpoint of a deletion. The chromosome result of a person with ring 18 might look something like this:

46,XY,r(18)

This indicates that the person has 46 chromosomes, and that one of the chromosome 18's has formed a ring. For a precise determination of the breakpoint, microarray analysis is required.

Ring chromosomes often occur in a mosaic form. So, you might see something that looks like this:

46,XY,r(18)[15]/46,XY[10]

This shows that 15 of the cells analyzed had the ring chromosome. The remaining 10 did not have the ring 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 not visible under a microscope. Because this is a more expensive test, it is often not the first test ordered during a diagnostic workout. 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 ring 18 might look something like this:

arr 18pterp11.21(12,842-2,541,233)x1; arr 18q22.3qter(71,215,307-78,077,000)x1

In the example above, "18p11.32q11.21 and 18q22.3qter" tell us that the breakpoints occur in 18p11.21 and 18q22.3 and extend to the end ("*ter*minus") of the chromosome arms. 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 18p deletion extends from the tip of the chromosome to base pair 2,541,233. The 18q deletion extends from base pair 71,215,307 to the end of the chromosome.

Note that microarray is not able to tell us with certainty that there is a ring chromosome present. Rather, this result simply tells us that a piece of the long arm as well as a piece of the short arm is missing. In order to see the changed chromosome arrangement, a routine chromosome analysis is necessary.

Key Genes and Critical Regions

Genes are located on the chromosome. Genes are the instructions that tell our bodies how to grow and develop. They do this by coding for proteins that do everything from aiding in digestion to determining hair and eye color. Because we have two copies of each chromosome, we also have two copies of each gene; one on each chromosome. When a piece of a chromosome is deleted, any genes in that region are missing. For many genes, it does not matter if one of the copies of the gene is missing. However, we know that when certain genes are missing, there can be medical and developmental effects.

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 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.

Because people with ring 18 typically have pieces of both 18p and 18q missing, we must consider genes that are located on both 18p as well as 18q.

Genes on 18p:

TGIF1 (3,451,591-3,458,406): Holoprosencephaly. This gene is located in chromosome band 18p11.31. About 10% of individuals who are missing one copy of *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.

Other individuals may have milder forms of the condition. For example, an MRI may show that their brain has minor changes, such as a missing corpus callosum (the connection between the two halves of the brain). There may be changes in the facial features as well, such as a cleft lip and palate or hypotelorism (eyes that are closely set to one another). Another minor feature of holoprosencephaly is a single incisor (front tooth) located at the midline of the mouth.

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 with one copy ofthis gene will develop dystonia. As research advances, we hope to better understand the risk of dystonia in individuals with one copy ofthis gene.

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

Genes on 18q:

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 will 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 one copy 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 *TSH1* 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 one copy is 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 and 18q.

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 life 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 is a birth defect in which the lower part of the spine does not form properly. About 7% of individuals missing this part of 18p- have sacral agenesis. There are varying degrees of severity. Some individuals may use wheelchairs while others are able to walk. Some may have incontinence, while others may have no symptoms.

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 is a gland 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.

Critical Regions on 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 (73,107,903-75,158,616): 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- 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 ring 18 that have not yet been linked to specific genes or regions on 18q or 18p.

Neurological Changes

People with ring 18 may have neurological problems beyond those discussed above. In particular, people with ring 18 frequently have low muscle tone (hypotonia).

If there are neurological concerns, a person should be referred to a neurologist for a complete evaluation.

Eyes and Vision

In addition to the ptosis and strabismus mentioned above, there are several other vision concerns that have occurred in people with ring 18. Sometimes, people with ring 18 have nystagmus, or involuntary eye movements. Near-sightedness, far-sightedness, and astigmatism also happen fairly frequently in people with ring 18. Colobomas (defects in the structure of the eye) and optic nerve hypoplasia (underdevelopment of the nerve that transmits information from the eye to the brain) have also been reported.

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

Heart

As mentioned above, tetralogy of Fallot has been linked to a specific region on 18p. However, there are other types of heart defects that have been reported in babies with ring 18 as well. In fact, the most common type of heart defect in children with ring 18 appears to be a septal defect. This means that there is a defect in the wall that separates the left and right sides of the heart.

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

Gastrointestinal Issues

It is not uncommon for people with ring 18 to have some gastrointestinal problems, including reflux and constipation. Dietary changes and medication may help. In severe cases of reflux, surgical intervention may be recommended.

Genitourinary Issues

As mentioned above, kidney problems have been linked to deletions of chromosome 18. Several different kinds of kidney problems have been described in children with ring 18. For example, they may have a small or a missing kidney. Urine may not be eliminated correctly, resulting in an abnormal accumulation of urine in the urinary system. This may lead to infections in the urinary tract.

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. In some instances, surgery is required to correct cryptorchidism or hypospadias.

Musculoskeletal Problems

Scoliosis and kyphosis have both been linked with changes on chromosome 18, as discussed above. In addition, people with ring 18 frequently have problems with their feet or back. For example, they may have a club foot or other kind of foot abnormality.

People with foot 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 ring 18 are often small for their age. Growth hormone deficiency has been linked to both 18p- and 18q-; identified in some people with ring 18, though the precise frequency of this finding is unknown.

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 Communiqué, Spring 1999.

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

Facial Features

People with ring 18 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 ring 18 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 or their eyes might be placed further apart than people without ring 18. The lower jaw may be slightly smaller than in people without ring 18.

Although people with ring 18 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 Ring 18, one of the family's first questions is often, "What does this mean for my child's lifespan?" This is a very important question. In general, if a person with Ring 18 is in good health with no major birth defects, there is no reason that they should not live to adulthood. In fact, within the Chromosome 18 Clinical Research Center, three out of the 25 study participants are over 18 years old. However, there have been at least two instances of premature death in a person with ring 18. One child passed away at 4½ years due to lung failure. Unfortunately, no additional medical records are available for this individual. There was another young participant who died at 5 years old. Although the official cause of death is unknown, this child had a history of hydrocephalus and heart problems as well as breathing difficulties, all of which may have contributed to his death. It is important to remember that early death in this population is the exception rather than the rule.

Development and Behavior

Individuals with ring 18 frequently have developmental and behavioral concerns in addition to the medical issues discuss above. However, it can be difficult to determine the "typical" presentation for individuals with ring 18. This is because they have both 18p- and 18q-. In addition, all people with ring 18 have different deletions, further complicating our ability to predict outcome. That being said, the Chromosome 18 Clinical Research Center does have some data on developmental outcome in people with ring 18.

The degree of impairment depends greatly on whether or not the deletion on 18q includes *TCF4,* the gene linked with Pitt-Hopkins syndrome.

Recommendations for Screenings and Referrals

Based on our current understanding of ring 18, there are several evaluations that we would suggest families consider for anyone recently diagnosed with ring 18. 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 or other neurologic issues 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 ring 18?"

In the grand majority of cases, the ring chromosome is a *de novo* event. That means that it is a unique change that only occurs in that individual. Siblings do not have a significantly increased risk to have ring 18.

If a person with ring 18 has a child, there is a chance that their child would have ring 18 as well. 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 ring 18 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

NSGC