THE CHROMOSOME 18
REGISTRY & RESEARCH SOCIETY

Distal 18q-: The Basics

Just Diagnosed with Distal 18q-

Receiving a diagnosis of distal 18q- can be a very difficult and confusing experience for families. Although it may explain why a child has medical problems or developmental delays, it also brings a lot of new questions. The good news is that we know a lot about distal 18q-, and we are continuing to learn more through the ongoing research at the Chromosome 18 Clinical Research Center.

We also encourage you to speak with a genetics provider in your area to learn more about what this diagnosis means for you and your family.

What is distal 18q-?

Distal 18q- happens when a piece of the long arm of one of the two copies of chromosome 18 is missing. This means there is one copy instead of two for each of the genes in the deleted region of the chromosome. This condition is different from another condition called proximal 18q-. Distal 18q- is caused by a deletion that is closer to the end of the chromosome and often includes the tip of the chromosome.

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

What causes distal 18q-?

Distal 18q- occurs when a piece of chromosome 18 is lost. This change likely occurred in the egg or sperm prior to conception or very shortly after conception. There is no known cause of distal 18q-.

How is distal 18q- diagnosed?

Distal 18q- is usually diagnosed when an infant or child has health and/or developmental concerns. Most often, the diagnosis is made by a blood test. This test looks at the chromosomes to see whether a piece of chromosome is missing.

Learn more about the diagnosis of distal 18q- on page 7

What problems are associated with distal 18q-?

Some babies with distal 18q- may have health problems that are noticeable at birth. For example, they may have a heart or a foot defect. They may have a hole in the roof of their mouth, known as a cleft palate. They may have breathing or feeding difficulties during the neonatal period. Other health problems frequently develop as babies with distal 18q- get older. In particular, people with distal 18q- have a higher likelihood of having hormone abnormalities, seizures, kidney problems, and changes in their immune system. They often have hearing and vision problems. There are other health problems that have been reported in people with distal 18q-, but these are the most common.

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

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

Are there any concerns for development in people with distal 18q-?

Most children with distal 18q- have developmental delays. This means that they do not meet their milestones on time, but they do achieve them. For example, they may roll over, walk, and talk later than other children. Almost all people with distal 18q- will have some intellectual or learning disability. This means they will have more difficulty learning and developing new skills. The degree of intellectual disability varies greatly. If the deletion includes a certain gene (TCF4), the intellectual disability is usually more significant.

How does Pitt-Hopkins syndrome relate to distal 18q-?

Pitt Hopkins syndrome is a condition that is caused by a small change impacting one gene on the long arm of chromosome 18: TCF4. Some people with distal 18q- have deletions that include TCF4. These individuals often have features of Pitt Hopkins syndrome, including changes in breathing patterns, a higher likelihood of seizures, and lack of speech, and more significant intellectual disability. For more information about Pitt Hopkins syndrome, visit the Pitt Hopkins Research Foundation.

What do the genes on chromosome 18 do?

There are about 100 genes in the area affected by distal 18q-. They play various roles in a person's growth, development, and overall health. Currently, research is focused on understanding how missing specific genes on chromosome 18 lead to health and developmental concerns. We know that many of the genes on 18 do not cause problems when one copy is

missing. However, there are a handful of genes that we think may be associated with specific features.

Learn more about genes of interest on distal 18q on page 12

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

It is difficult to predict how an individual will be affected by a deletion of distal 18q. However, we know that children with distal 18q- go to school, develop new skills, make friends, and are active members of their communities.

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

Every child with distal 18q- is different. However, we can make some recommendations for evaluations to ensure that the most common concerns are identified and addressed early. The Chromosome 18 Clinical Research Center has created a "Distal 18q- Management Guide". We strongly recommend reviewing this document for additional details and information about managing distal 18q-. Some of the management recommendations include the following:

Immediate Referrals to:

- Genetics
- Early Intervention

One Time Evaluations:

- Echocardiogram
- Abdominal ultrasound

Annual Screenings:

- Ophthalmology
- Hearing
- Thyroid

Closely Monitor:

- Growth and development
- Changes in neurological status
- Allergy and autoimmune symptoms

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 Distal 18q-

As you may already know, distal 18q- occurs when there is a deletion on the long arm of chromosome 18. You may also be wondering what, precisely, this means.

On this page, we will discuss some basic genetic concepts. However, we also recommend that families meet with a genetics professional, such as a geneticist or a genetic counselor, to talk about the genetic basis of distal 18q-. A genetics professional will also review the specific genetic change that was identified in the family.

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

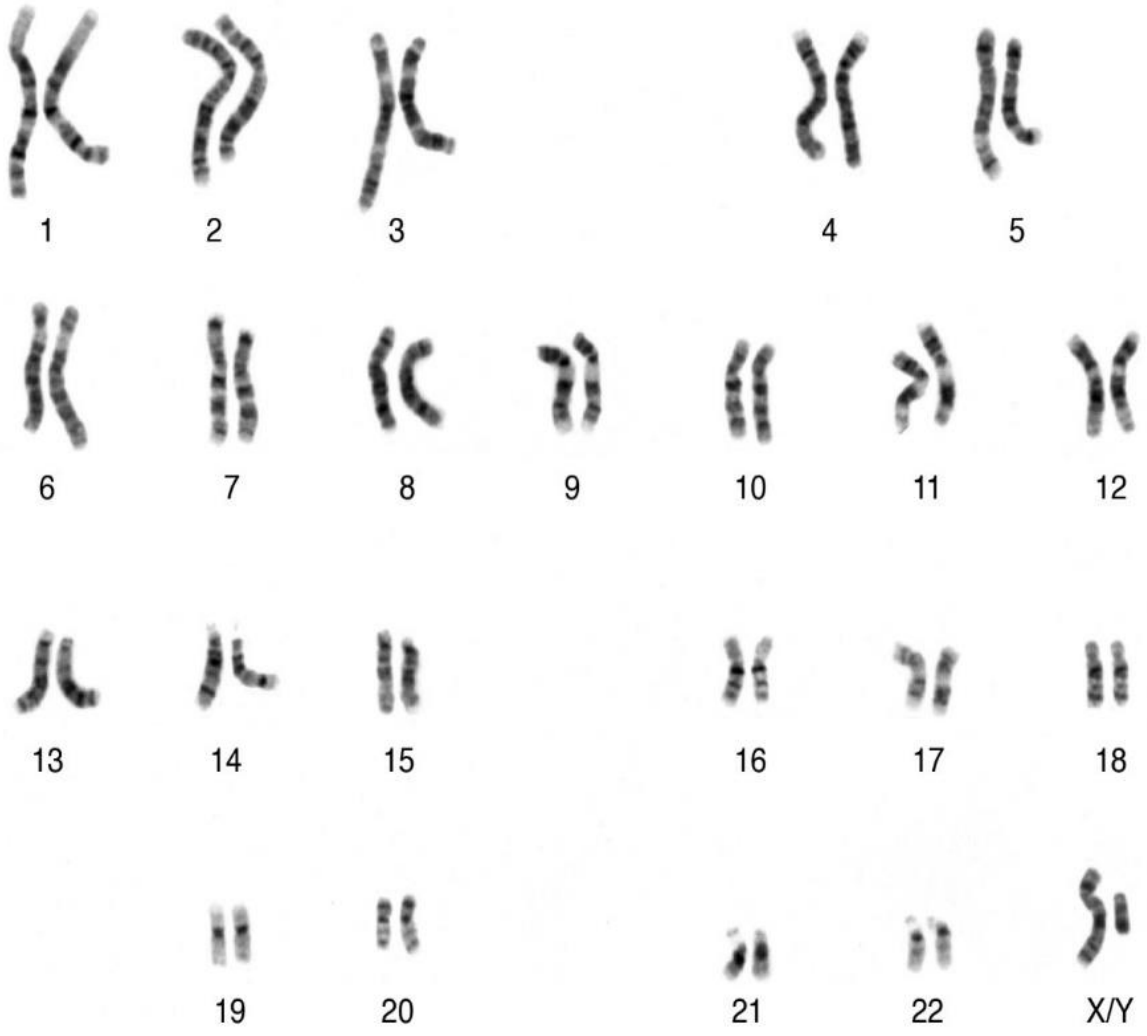
Genes and Chromosomes:

You have probably heard the word "gene" or "genetic" before, but what is a gene, and how does it relate to health? Put simply, a gene is an instruction. **A gene tells our body how to make a certain protein**. Those proteins, in turn, have many different functions throughout our bodies. Our genes determine many physical features, such as skin, hair, and eye color. Genes also give instructions for proteins that are not so obvious to the naked eye. For example, genes play a role in fetal development, telling the cells and tissues how to form different organs. Genes also continue to play a role after birth, coding for proteins that are involved in day-to-day functions, such as the metabolism of food. **When a gene is changed or is missing, it may affect the**

protein it is supposed to make, which may, in turn, lead to physical differences or medical and developmental concerns.

Genes are located on the chromosomes, similar to the way that beads may be strung along a necklace. The chromosomes are located in nearly every cell of the body. Each of these cells carries 23 pairs of chromosomes, for a total of 46 chromosomes. We inherit one set of 23 chromosomes from each parent. This means we have two copies of each chromosome, one from our biological mother and one from our biological father. **Because the genes are located on the chromosomes, we typically also have two copies of nearly all of our genes**.

Chromosomes are not visible to the naked eye. However, it is possible to view the chromosomes under a microscope. You can see that each chromosome is unique in its size as well as the striped pattern (known as banding). These differences are noticeable to a trained eye.



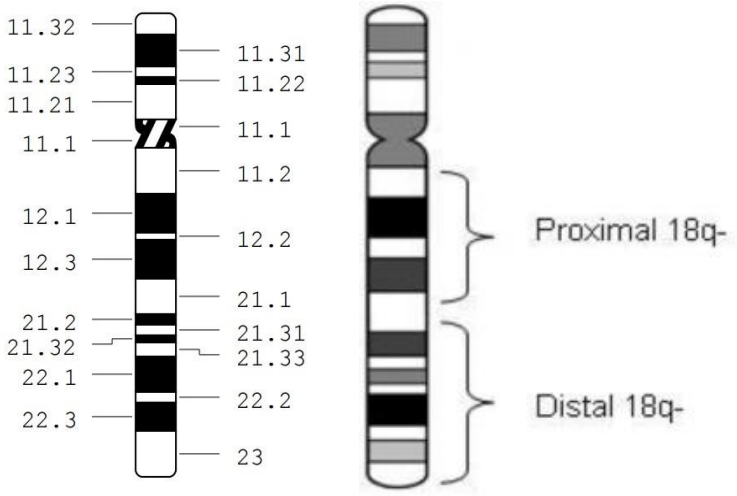
In addition to the characteristic banding pattern, chromosomes have different locations of the centromere. The centromere is a tiny constriction somewhere along the length of the chromosome. This constriction divides the chromosome into two different segments. These segments are called arms. The shorter arm (called "p" for petit) is always shown on top. The longer arm is called the "q" arm and is shown below the p arm.

Distal 18q- occurs when there is a missing piece, known as a deletion, on the q arm of chromosome 18. Because the genes are located on the chromosomes, the genes that are located within the deletion are also missing. **In other words, a deletion means that only one copy of the gene is present rather than two**. This is what leads to the health and developmental concerns associated with distal 18q-.

Difference between proximal and distal 18q-

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

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



18q-: Diagnosis

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

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

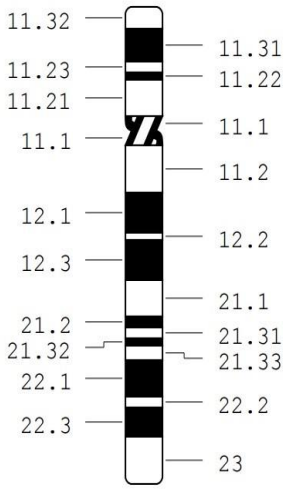
On rare occasions, 18q- may be detected before a baby is born. However, it is usually diagnosed during infancy or childhood. There are two tests that are commonly performed to identify a deletion on 18q. Both of these tests are usually performed on a blood sample.

Routine Chromosome Analysis

In this test, white blood cells are grown in the lab. The chromosomes are stained and examined under a microscope by a qualified cytogeneticist. This individual is trained in recognizing extra, missing, and rearranged pieces of chromosomes. Results from a chromosome analysis will tell us the number of chromosomes, whether the person is a male or a female, and which bands of the chromosome are involved in the change. The chromosome result of a person with proximal 18q- might look something like this:

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

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



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

Microarray Analysis

A microarray analysis is similar to a routine chromosome analysis in that it can tell us if there are extra or missing pieces of a chromosome. However, microarrays can detect chromosome deletions and duplications that are too small to be visible under a microscope. Therefore, it is a much more precise test than a routine chromosome analysis. A microarray result can tell us with great specificity which genes are included in the deletion.

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

Distal 18q-: Health Concerns

This page describes some of the most common health problems that have been reported in people with distal 18q-. It is important to remember that these concerns do not occur in everyone with distal 18q-. Also, we do not discuss treatment options or recommendations on this page. It is important that you speak with your team of healthcare providers to make a plan to check for and manage health concerns. In addition, the Chromosome 18 Clinical Research Center has developed Management Guidelines. These documents have more detailed information about the health problems seen in people with distal 18q-, including how frequently they occur. They also include specific recommendations about checking for health issues.

Lastly, it is important to understand that people with distal 18q- may develop health problems that are not listed on this page. As research on the chromosome 18 conditions continues, we will learn more about what to expect for people with distal 18q- and how to help them stay healthy and live productive, fulfilling lives.

Birth Defects

Babies with distal 18q- may develop differently in the womb, leading to birth defects. Different types of heart defects have been reported in babies with distal 18q-. Foot abnormalities, such as rocker bottom foot and clubfoot, are also common. Babies with 18q- may also have an opening in the roof of their mouth, called a cleft palate. They may or may not also have a cleft lip.

Hernias have been reported in some newborns with distal 18q-. A hernia occurs when some

organs, often the intestines, push outside of the abdomen into another part of the body. Both inguinal (involving the groin region) and umbilical hernias (involving the umbilical opening) have been seen in babies with distal 18q-.

Problems in the Newborn Period

Newborns with distal 18q- may have problems at or shortly after birth. They may have feeding difficulties. For example, they may have problems latching onto the breast or bottle. They may also have problems coordinating the suck-swallow motion that is required to nurse. Some infants may vomit frequently after eating. If they have a cleft or a high arched palate, they may have additional difficulties feeding.

Infants with distal 18q- may also have jaundice. Jaundice is a build-up of bilirubin in the baby's blood, leading to a yellowish color of the skin and eyes.

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

Neurological Changes

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

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

Almost everyone with distal 18q- has a decreased amount of myelin in the central nervous system. This is called dysmyelination and can only be identified with an MRI. Myelin is a substance that covers nerve cells similar to the way that plastic coating covers a wire in an electric cord. The myelin helps transmit electrical signals to and from the brain. At this point in time, we do not know if or how these changes in the amount of myelin affect a child's development. We suspect that it slows an individual's reaction time. For example, it might take a person with distal 18q- longer to understand an instruction or to respond to a question. Dysmyelination may also contribute to attention problems, anxiety, and depression.

Eyes and Vision

People with distal 18q- frequently have vision problems. In particular, strabismus and nystagmus can be associated with distal 18q-. Strabismus occurs when the movements of the eyes are not coordinated with each other. This is frequently referred to as being "cross-eyed". Nystagmus describes repetitive and uncontrolled movements of the eyes. In addition, near-sightedness is seen in some people with distal 18q-.

Hearing

Children with distal 18q- have a higher likelihood of having hearing loss. There are two types of hearing loss. Conductive hearing loss describes hearing loss that is caused when there is an obstruction to the transmission of sound from the outer ear to the inner ear. People with distal 18q- often have narrow ear canals; some people's ear canals are completely closed. This can lead to conductive hearing loss. Recurrent ear infections are another cause of conductive hearing loss.

The second type of hearing loss is called sensorineural hearing loss. This refers to a hearing loss that is caused by a change in the nerves that transmit signals from the ear to the brain.

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

Gastrointestinal Changes

Babies and children with distal 18q- may have some problems with digestion. The most common digestive problem is reflux. This occurs when the stomach contents flow upwards. This can cause pain, irritability, and vomiting.

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).

Some people with distal 18q- may have kidney problems. This can affect both males and females. Vesicoureteral reflux frequently happens in people with distal 18q-. This occurs when urine flows from the bladder up towards the kidneys. This is known as vesicoureteral reflux and can lead to recurrent urinary tract infections and kidney damage. In addition, some people have structural changes in the kidney.

Skeletal Changes

In addition to foot abnormalities that are present at birth, some people with distal 18q- may have flat feet or toes that overlap each other. Some develop an abnormal curvature of their spine (scoliosis or kyphosis). People with distal 18q- may have "bow-leggedness" (genu varum). All of these bone problems can affect the way they walk and may lead to gait abnormalities.

Growth Changes

Children and adults with distal 18q- may have changes in their growth patterns. They are often small for their age. This is frequently 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.

Endocrine Changes

Some people with distal 18q- have changes in their hormone levels. These include growth hormone deficiency (discussed above). Thyroid abnormalities are also fairly common in people with distal 18q-. Low thyroid is the most common thyroid change. Symptoms of low thyroid include fatigue, weight gain, and depression.

Immunology

Low levels of IgA are found in some people with distal 18q-. 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 than those with normal levels of IgA.

Recently, we have also learned that people with distal 18q- seem to have a higher incidence of autoimmune conditions. Autoimmune conditions are a group of disorders that are caused when the immune system mistakenly attacks the body. Lupus, arthritis, and Sjogren syndrome have all been reported in people with distal 18q-.

Psychiatric Changes

We have learned that people with distal 18q- often develop anxiety and/or depression during adolescence.

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:

We are still collecting information about lifespan in individuals with distal 18q-. However, we

know that people that are missing the TCF4 gene have a higher risk for early death. This group is often more complicated from both a medical and a developmental standpoint, and they are more susceptible to infections and other problems.

Genes of Interest on Distal 18q

Here, we will talk about genes on distal 18q that have been linked to specific health concerns. It is important to have an understanding of basic genetic concepts. You can read about genes and chromosomes here.

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

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

SMAD4: 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: 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.

TSHZ1: Aural Atresia and Stenosis
This gene is associated with one of the most common features of distal 18q-: aural atresia and stenosis (narrow or closed ear canals). It is located in chromosome band 18q22.3. About 80% of people with deletions that include TSHZ1 have narrow or absent ear canals.

Contact Us

210.657.4968
7155 Oakridge Drive
San Antonio, Texas 78229

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."