Pitt-Hopkins Syndrome

Background and Genetic Basis

Historically, the Chromosome 18 Registry & Research Society has been composed of families of people with large deletions and duplications of chromosome 18. However, thanks to recent advances in technology, smaller, submicroscopic changes of chromosome 18 are now detectable. Pitt-Hopkins syndrome (PTHS) is a condition caused by such a change. The goal of this page is to describe the major features of Pitt-Hopkins syndrome. This information was obtained from a thorough review of the literature as well as information from the Pitt Hopkins Syndrome Support Group (http://groups.google.com/group/pitt-hopkins/) and the Pitt Hopkins Syndrome International Network (http://www.pitthopkins.org/). This information may help you and your healthcare team make decisions about how to care for a person with PTHS.

Our Mission:

To help individuals with chromosome 18 abnormalities overcome the obstacles they face so they might lead healthy, happy, and productive lives.

Background

Pitt-Hopkins syndrome was first described by two physicians in 1978. Until recently, the diagnosis of PTHS was based on a person's medical history and a physical examination. New technology has allowed scientists to identify the genetic cause of PTHS. Now, the diagnosis of PTHS is usually based on the results of microarray analysis or gene sequencing. Both tests can be performed on a blood sample.

Genetic Basis

PTHS is caused by a mutation within or a complete deletion of the *TCF4* gene. Genes are the instructions that tell the body how to grow and develop. Genes are located on the chromosomes. For more information about genetics, please visit our website at www.chromosome18.org.

Deletions and changes (also called mutations) in the *TCF4* cause the gene to stop working properly. The body is then missing an important instruction. This leads to the medical and developmental problems associated with PTHS.

Unlike the other conditions discussed on this website, PTHS is not diagnosed with a chromosome analysis. More specialized testing, such as microarray analysis or sequencing, is required.

Recently, there has been a paper suggesting that changes in the *CNTNAP2*and *NRXN1* genes are responsible for medical and developmental features similar to those found in Pitt-Hopkins syndrome. The information on this page refers solely to PTHS caused by mutations or deletions of the *TCF4* gene.

An Evolving Understanding

Now that the genetic cause of PTHS has been identified, it is much easier to make the diagnosis. A simple blood test can confirm the diagnosis. This allows clinicians to identify people who do not fit the original description of PTHS. We are learning that there is more variability in this condition than originally thought. For example, we are learning that the range of intellectual ability is wide, with some individuals functioning in the moderate range of impairment. As time goes on and more individuals with PTHS are identified and described, our understanding of this condition will grow and change as well.

18q- and PTHS

The *TCF4* gene is located on the long arm of chromosome 18. Some individuals that have distal 18q- are missing the *TCF4* gene. These individuals often have similar findings to patients with PTHS. However, we usually still refer to these individuals as having 18q-. This is because, in addition to the features of PTHS, they may also have features commonly associated with distal 18q-, such as growth hormone deficiency and narrow ear canals.

Families with 18q- may wonder whether or not their deletion includes the *TCF4*gene. It may be difficult to answer this question. In most cases, 18q- was diagnosed using a routine chromosome analysis. This type of analysis can only give a general idea of the location of the deletion's breakpoint. It cannot tell us precisely which genes are or are not deleted. In order to have this information, a more specialized test, called a microarray analysis, is required.

Characteristics of PTHS

Development and Behavior

PTHS changes the way the brain develops and functions. Infants, toddlers and children with PTHS develop more slowly that those without PTHS. For example, it will take longer for them to roll over, sit, crawl, and walk. It will take longer for them to reach for and grab toys, hold a bottle, and to feed themselves.

People with PTHS have some degree of mental impairment. Usually, the degree of mental impairment falls into the moderate to severe range of impairment. Many will learn to walk during childhood. They may have a wide-based, unsteady gait. Speech also typically develops more slowly than in babies that do not have PTHS. Although many people with PTHS do not talk, many are able to understand language and communicate with hand gestures, words, or short sentences.

Many of the children that have been diagnosed with PTHS have repetitive motions and movements. For example, they may flap their hands or rock themselves. In general, they are described as having happy dispositions. In fact, many people with PTHS are at first thought to have Angelman syndrome, another genetic condition that causes many of the same medical and developmental concerns.

Some individuals with PTHS have ataxia. People with ataxia usually have a hard time coordinating the movement of their arms and legs. It may make walking more difficult.

One of the most unique characteristics of PTHS is an abnormal breathing pattern. That is, many individuals with PTHS have episodes where they breathe more quickly or more frequently than normal. This may lead to light-headedness; fainting; numbness and tingling in the hands and feet; and abdominal discomfort.

Neurologic changes

People with PTHS often have some changes in their muscle tone. Most often, they have decreased muscle tone. This is called hypotonia. 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. Low muscle tone may also contribute to developmental delays. Physical, occupational, and speech therapy may improve hypotonia.

Seizures are fairly common in people with PTHS. 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.

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MRI findings

Many people with PTHS have changes in the brain that can only be detected with an MRI. The most common change is a small corpus callosum. The corpus callosum is a bundle of nerves that connects the left and the right side of the brain. This can be associated with some of the neurological problems described above.

Changes in the caudate nucleus have also been reported. The caudate nucleus is a part of the brain involved with learning and memory. The effects of these changes are not well-understood.

Eyes and vision

Vision problems are common in people with PTHS. The eyes may be crossed (strabismus). Nearsightedness (myopia) has also been reported. Because vision problems are possible, people with PTHS should have regular eye exams.

Orthopedic

People with PTHS may have a curvature of the spine (scoliosis). Foot abnormalities are also fairly common. The most common foot problem is flat feet (pes planus). However, other foot changes have been noted. For example, many people with PTHS have small and slender feet.

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

Genitourinary

Males with PTHS may have some changes in the genital region. The testicles may not be fully descended (cryptorchidism). In some cases, this may require surgical correction.

Growth

In general, people with PTHS are shorter than other children and adults of the same age. In addition to short stature, many people with PTHS have microcephaly, or a head size that falls below the 3rd percentile.

Facial Features and Other Findings

People with PTHS 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. Their cheekbones might be higher than other family members'. The mouth may be wider and the lip might be shaped a little differently. The teeth might be slightly widely-spaced. The lower part of the face might extend slightly beyond the upper part of the face. Although people with PTHS 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.

Another feature that has been reported in some people with PTHS is an extra nipple. These are sometimes called accessory or supernumerary nipples. They have no health implications. In fact, they occur fairly regularly in the general population. That is, they are frequently found in people who do not have a genetic condition.

Family Planning and Genetic Counseling

Many parents wonder, "If we have another child, what is the chance that our next child will have PTHS?"

In general, the likelihood that a second child will also have PTHS is low. However, there has been one case report in which the mother of a child with PTHS was found to have the same genetic change in some of her cells. In this case, there is a significant chance that a second child could be born with PTHS.

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

For Additional Information and Support

The information provided here is general information based on the literature as well as the experiences of the Pitt Hopkins Syndrome Support Group and the Pitt Hopkins Syndrome International Network. However, every person and family with PTHS 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 (http://www.ncbi.nlm.nih.gov/sites/GeneTests/clinic)

National Society of Genetic Counselors (www.nsgc.org)

Several families have come together to create an online support group. This group offers families an opportunity to share experiences and information in a private setting. The Pitt Hopkins Syndrome Support Group can be found at http://groups.google.com/group/pitt-hopkins/. Additional information about Pitt Hopkins syndrome as well as families' personal stories can be found at the Pitt Hopkins Syndrome International Network (http://www.pitthopkins.org/).

Selected References

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If you found this information helpful, or would like to learn more about the Chromosome 18 Registry & Research Society, we encourage you to become a member of our organization.

To become a member, visit our website at www.chromosome18.org or call us at 210-657-4968.

With your help, we will achieve our mission :

To help individuals with chromosome 18 abnormalities overcome the obstacles they face so they might lead healthy, happy, and productive lives.