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The Role of Mutations on Gene TCF4, in Pitt-Hopkins Syndrome

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Pitt Hopkins Syndrome (PTHS) is a rare genetic and neurological disorder. Affected children have certain facial features, including mental retardation, developmental delays, impaired ability to speak, and recurrent seizures and respiratory pattern disorders. Other symptoms that may occur include poor coordination (ataxia), frequent non-functional hand movements, constipation, sleep disturbances, and severe myopia (myopia). Behavioral abnormalities are common, although children are often described as social and cheerful. Some children with autism spectrum disorders meet the criteria. The specific signs and symptoms of this disorder and their severity can vary from person to person. Pitt Hopkins syndrome is caused by a change (mutation) in the TCF4 gene. This mutation occurs spontaneously and is almost non-existent in a family. The disorder was first described in the medical literature in 1978, and its causative gene was discovered in 2008.

Keywords: Pitt Hopkins Syndrome; TCF4 gene; Atatxia; Epilepsy; Hyperventilation

Overview of Pitt-Hopkins Syndrome

Pitt Hopkins Syndrome is a genetic disease characterized by mental retardation and growth retardation, respiratory problems, recurrent seizures (epilepsy), and distinctive facial features. People with Pitt Hopkins Syndrome have moderate to severe mental disabilities. Most people with mental retardation delay the development of mental and motor skills (psychomotor retardation).[1]

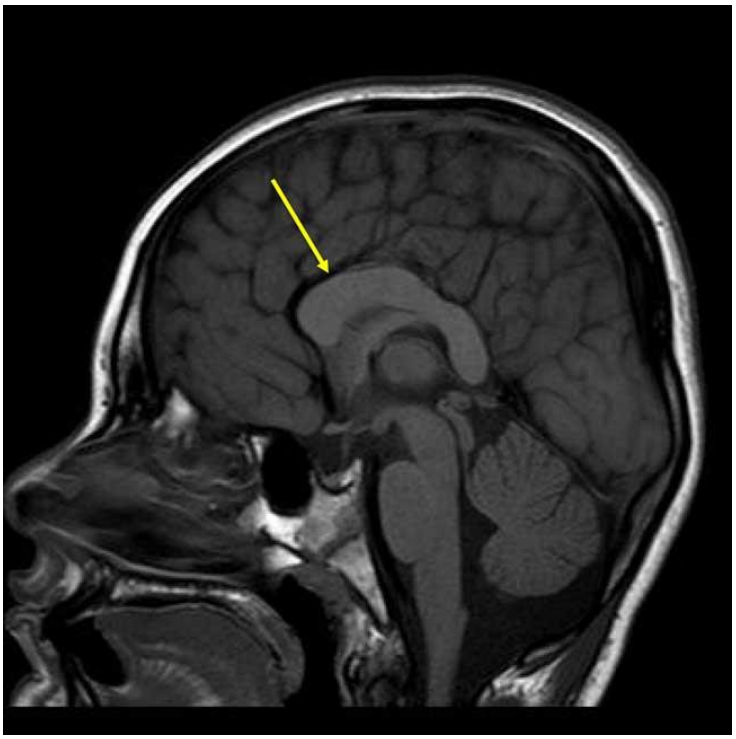


Figure 1: Radiographic image of a brain with Pitt-Hopkins syndrome.[1]

Clinical Signs and Symptoms of Pitt-Hopkins Syndrome

People with this syndrome have a delay in learning to walk and developing fine motor skills such as picking up small objects with their fingers. People with Pitt Hopkins syndrome are usually unable to speak. Some may learn to say a few words. Many people with the disorder exhibit features of autism spectrum disorders that impair communication and social skills.[1]

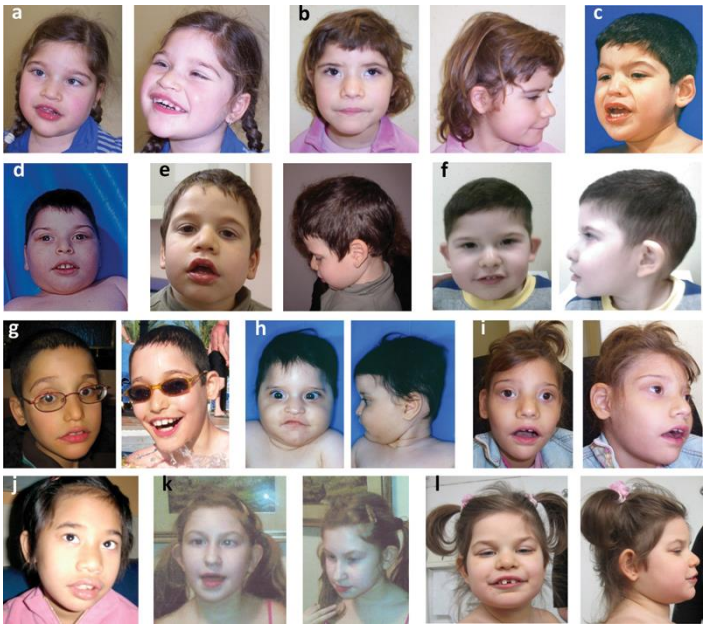


Figure 2: Images of Pitt-Hopkins syndrome patients with related disorders.[1]

Respiratory problems in people with Pitt Hopkins syndrome are characterized by periods of rapid breathing (hyperventilation) followed by periods of slow or stopped breathing (apnea). These periods can cause a lack of oxygen in the blood and lead to a bluish tinge to the skin or lips (cyanosis). In some cases, lack of oxygen can cause loss of consciousness. Some older people with Pitt Hopkins Syndrome have wide, round fingertips (clubfoot) due to frequent periods of hypoxia. Respiratory problems only occur when a person is awake and usually first appear in mid-childhood, but can start as early as childhood. Excessive breathing and apnea can be caused by emotions such as excitement or anxiety or excessive fatigue (severe fatigue).[1,2]

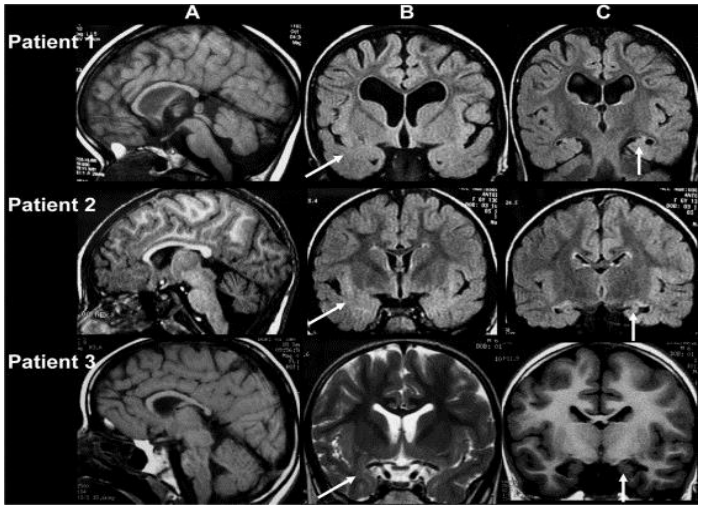


Figure 3: Radiographic image of a brain with Pitt-Hopkins Syndrome.[1]

Epilepsy also occurs in most people with Pitt Hopkins syndrome and usually begins in childhood, although it can be present from birth. People with Pitt Hopkins Syndrome have distinctive facial features that include thin eyebrows, sunken eyes, a prominent nose with a long nose bridge, a double raised curve on the upper lip (Cupid bow), a wide mouth with thick lips, and a long distance. The teeth are apart, and the ears are usually thick and cup-shaped.[1,2]

Children with Pitt Hopkins Syndrome typically have happy, irritating behaviors with frequent smiles, laughter, and touching gestures. However, they can also experience anxiety and behavioral problems. Other features of Pitt Hopkins syndrome include constipation and other gastrointestinal problems, small head size (microcephaly), myopia (not seeing distant objects), eyes that are not visible in one direction (strabismus or lochia). Eyes), short stature and minor abnormalities of the brain. Affected people may also have small hands and feet, a crease in the palms of the hands, flat feet (pes planus), or unusual fleshy pads on the tips of the fingers and toes. Men with Pitt Hopkins syndrome may have cryptorchidism.[1,2]

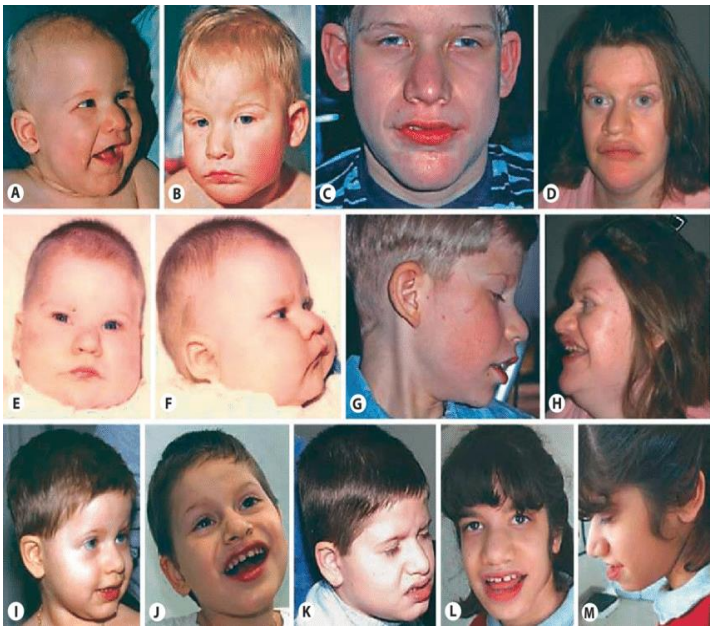


Figure 4: Another view of patients with Pitt-Hopkins syndrome with related disorders.[1]

Etiology of Pitt Hopkins syndrome

A mutation in the TCF4 gene, located on the long arm of chromosome 18 at 18q21.2, causes Pitt Hopkins syndrome. This gene provides the instructions for the synthesis of a protein that binds to other proteins and then binds to specific regions of DNA to help control the activity of many other genes. Based on DNA binding and gene control activities, the TCF4 protein is recognized as a transcription factor. The TCF4 protein is involved in the maturation of cells to perform specific functions (cell differentiation) and the destruction of cells themselves (apoptosis).[1,3]

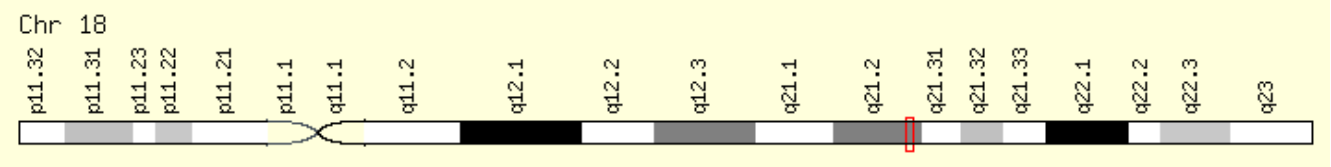
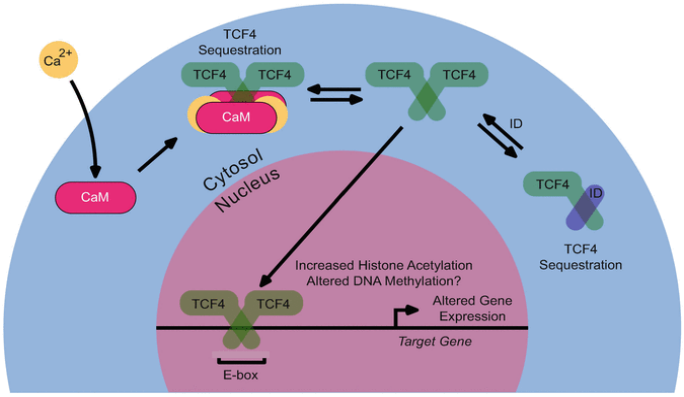


Figure 5: Schematic of chromosome 18 where the TCF4 gene is located in the long arm of this chromosome as 18q21.2.1

Mutations in the TCF4 gene impair the ability of proteins to bind to DNA and control the activity of specific genes. These disorders, especially the inability of the TCF4 protein to control the activity of genes involved in the development and function of the nervous system, contribute to the signs and symptoms of Pitt Hopkins syndrome. In addition, additional proteins interact with the TCF4 protein to perform specific functions. When the TCF4 protein is inactive, these other proteins are no longer able to function normally. It is also possible that the loss of normal proteins bound to non-functional TCF4 proteins may contribute to the characteristics of these conditions. Loss of a protein, particularly a protein synthesized by the ASCL1 gene, located on the long arm of chromosome 12 at 12q23.2, is thought to be associated with respiratory problems in people with Pitt Hopkins syndrome.[1,3]

Pitt Hopkins syndrome follows an autosomal dominant inheritance pattern. Therefore, a copy of the TCF4 mutant gene (either parent) is required to cause the syndrome, and the chance of having a child with the autosomal dominant syndrome is 50% for each possible pregnancy.[1,3]



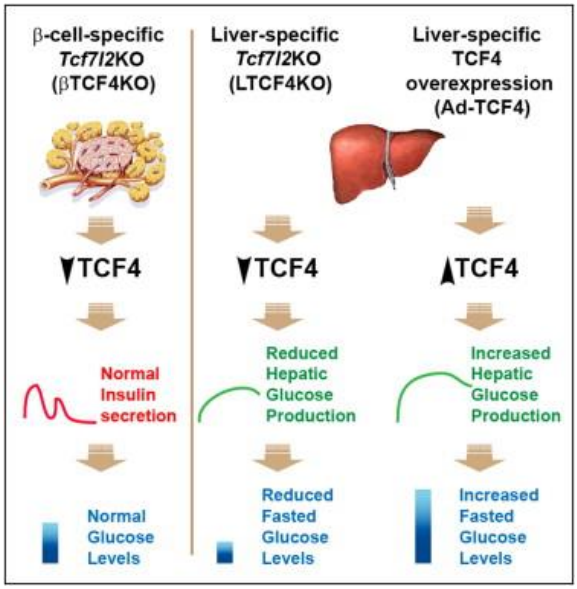


Figure 6: Schematic of the molecular and biochemical mechanism of the TCF4 gene in various organs of the body.[1]

Frequency of Pitt Hopkins Syndrome

Pitt Hopkins syndrome is thought to be a very rare genetic disease. So far, about 500 people with this syndrome have been reported in the medical literature from around the world[1,4].

Diagnosis of Pitt Hopkins Syndrome

Pitt Hopkins syndrome can be diagnosed based on the clinical and physical findings of patients and some pathological tests. The most accurate way to diagnose this syndrome is a molecular genetic test for the TCF4 gene to check for possible mutations.[1,4]

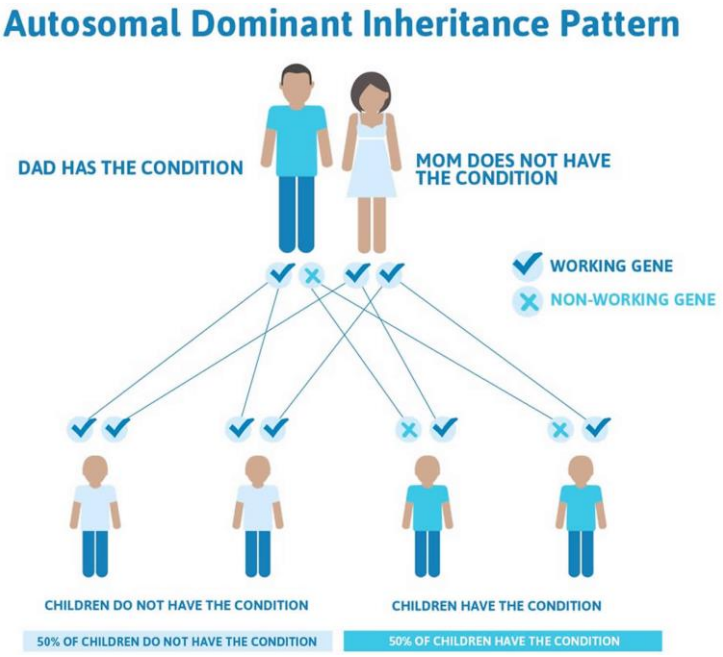


Figure 7: Schematic of the predominant autosomal inherited pattern that Pete-Hopkins syndrome follows.[1]

Treatments for Pitt Hopkins Syndrome

The treatment and management strategy for Pitt Hopkins syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including a pulmonologist, cardiologist, neurologist, oral and maxillofacial specialist, surgeons, and other health care professionals. There is no definitive treatment for this syndrome and all clinical measures are taken to alleviate the suffering of the patients. Genetic counseling is also essential for all parents who want a healthy baby.[1,4]

Discussion and Conclusion

Pitt Hopkins Syndrome is a genetic disease characterized by

mental retardation and growth retardation, respiratory problems, recurrent seizures (epilepsy), and distinctive facial features. People with Pitt Hopkins Syndrome have moderate to severe mental disabilities. Pitt-Hopkins syndrome is caused by an unexpected change (mutation) in the TCF4 gene.[1,5] Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, absent or overproduced. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain. The TCF4 gene creates a protein that is a transcription factor. This protein has an important role in various developmental processes of the body. It is highly expressed early during human development and is found throughout the central nervous system. The treatment and management strategy for Pitt Hopkins syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including a pulmonologist, cardiologist, neurologist, oral and maxillofacial specialist, surgeons, and other health care professionals.[1,6]

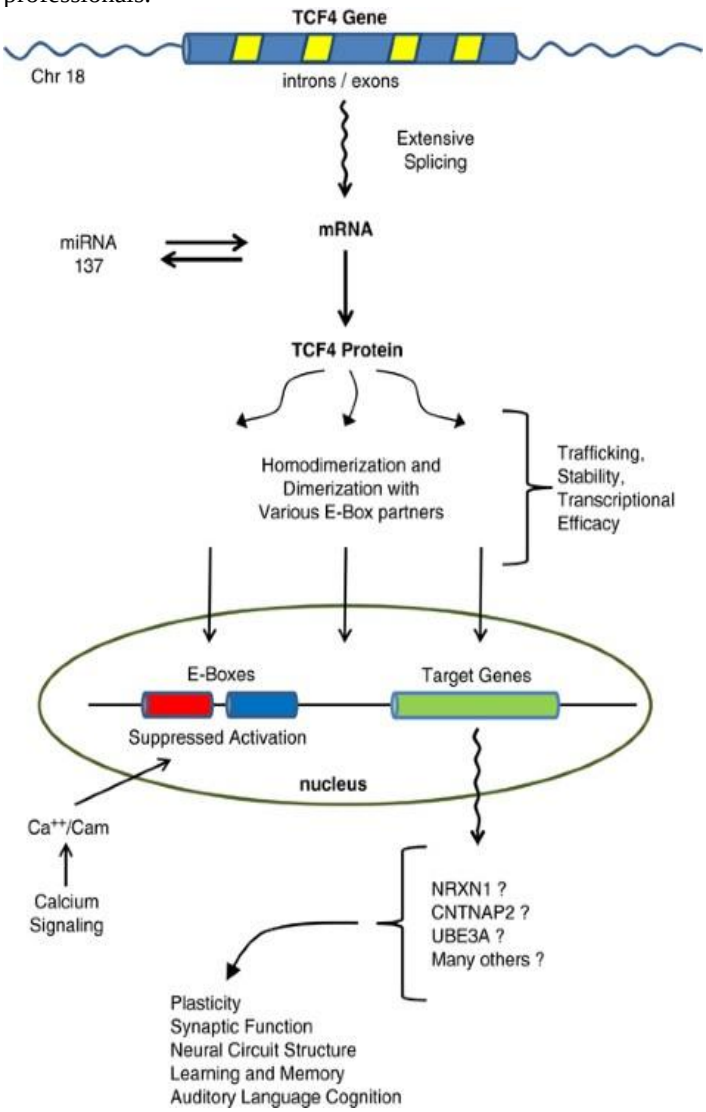


Figure 8: Schematic of the molecular pathway of the TCF4 gene.[1]

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