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Pitt-Hopkins Syndrome

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Introduction

Pitt-Hopkins syndrome is a rare neurodevelopmental disorder caused by loss of function of one allele of the *TCF4* gene. Most cases result from a *de novo* mutation that leads to a functional loss of one copy of the *TCF4* gene. Other cases result from a deletion of the chromosome region in which the *TCF4* gene is located (18q21.2).

Pitt-Hopkins syndrome is characterized by distinctive facial features (e.g., deep-set eyes, prominent nose, wide mouth with widely spaced teeth), global developmental delay, and moderate-severe intellectual disability. Breathing problems and epilepsy often occur.

Once Pitt-Hopkins syndrome has been suspected clinically, the diagnosis is confirmed by molecular genetic testing of the *TCF4* gene.

Characteristics

Pitt-Hopkins syndrome is rare—approximately 500 cases of Pitt-Hopkins syndrome have been reported worldwide (1). In infancy, low muscle tone can cause feeding problems. In older children, gait looks stiff because of a combination of low muscle tone (hypotonia) and balance problems (ataxia).

Children with Pitt-Hopkins tend to have a happy disposition, with hand flapping and excitability. They may develop abnormal breathing patterns, such as sudden attacks of hyperventilation followed by breath-holding until cyanosis. About half of these children have epilepsy; typically their ECG is normal (2). Subtle changes in the brain may be seen in up to 70% of patients by MRI (e.g., underdeveloped corpus callosum, dilated ventricles) (3).

Most adults with Pitt-Hopkins syndrome have severe cognitive impairment, and although they may vocalize, they are unable to use language. Other issues include gastrointestinal (e.g., constipation), ophthalmic (e.g., strabismus, severe myopia), and behavioral problems (e.g., anxiety, stereotypical movements of the head and hands).

Pitt-Hopkins syndrome may be distinguished clinically from other causes of intellectual disability and developmental delay (e.g., Angelman syndrome, Rett syndrome, Mowat–Wilson syndrome) by: 1) abnormal breathing patterns (onset from 7 months to 7 years); 2) lack of congenital abnormalities; and 3) distinctive facial features (craniofacial dysmorphism). In infants, the first sign of craniofacial dysmorphism may be the prominence of the nose and lower face. As the child grows, they may develop deep-set eyes, a high nasal root

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with prominent nasal bridge, wide nostrils and down-turned nasal tip; a short philtrum, and a wide mouth with widely spaced teeth.

Genetics

Pitt-Hopkins syndrome is an autosomal dominant disorder caused by haploinsufficiency of the *TCF4* gene. Haploinsufficiency occurs when one copy of the gene has been lost (e.g., by a loss-of-function mutation), and the remaining copy of the gene is not sufficient to prevent the disorder.

TCF4 has an important role in the development of the nervous system. *TCF4* encodes a transcription factor—a protein that binds to specific DNA sequences and controls the expression of other genes. The TCF4 protein contains a basic helix-loop-helix (bHLH) domain, and is also known as an "E-protein" because it binds to a specific sequence of DNA known as an "E-box".

The TCF4 protein is expressed in the brain, heart, lungs, and muscles. TCF4 is also active during early human development, when it is thought to be involved in a series of developmental processes, including initiating the development of several regions of the nervous system (3).

Mutations in *TCF4* disrupt the ability of the protein to bind to DNA and initiate neuronal differentiation, contributing to the neurological symptoms seen in Pitt-Hopkins syndrome. In addition, other proteins that normally form heterodimers with TCF4 are unable to function normally. One of these proteins, ASCL1, is thought to be involved in development in the brain stem—after defective interaction with TCF4, impaired development of the brain stem may contribute to the breathing problems that characterize Pitt-Hopkins syndrome (3).

A spectrum of mutations can disrupt the *TCF4* gene, which is located on the long arm of chromosome 18 (18q21.2) (4, 5). The gene has 20 exons, of which exons 2 to 19 are coding. Exon 18 is thought to harbor a quarter of disease-causing mutations (6).

Approximately 30% of cases of Pitt-Hopkins syndrome are caused by whole gene deletions of TCF4, and approximately 10% caused by partial gene deletions. Missense mutations are also common, and mainly involve the bHLH domain, whereas nonsense and frameshift mutations are spread throughout the gene. Splice site mutations are less common (approximately 10%), and balanced translocations are a rare cause of Pitt-Hopkins syndrome (3, 7).

Diagnosis

The diagnosis of Pitt-Hopkins syndrome is based on the clinical presentation and confirmed by molecular genetic testing.

Currently, there is not a generally accepted diagnostic criteria, but the hallmarks of the syndrome that support a diagnosis of Pitt-Hopkins syndrome are facial dysmorphism, early onset global developmental delay, moderate to severe intellectual disability, seizures, breathing abnormalities, and a lack of major congenital abnormalities (2, 3, 8).

Management

Infants with Pitt-Hopkins syndrome should receive treatment from a multidisciplinary team specializing in the care of children with cognitive and motor impairment, including physical therapists, occupational therapists, and speech therapists. Medical specialists for pulmonary conditions, epilepsy, gastrointestinal conditions and other medical issues may also be needed.

Genetic Testing

The NIH Genetic Testing Registry, GTR, provides examples of the genetic tests that are currently available for Pitt-Hopkins syndrome and the *TCF4* gene.

Testing options include sequence analysis (to determine the nucleotide sequence of *TCF4*), chromosome microarray analysis (to detect copy number variants by determining the gain or loss of chromosome material), quantitative PCR (to determine the relative amount of DNA or RNA in a sample), and cytogenetic testing/karyotyping (to assess chromosome number and structure).

Sequencing analysis detects approximately 70% of *TCF4* variants, which may include missense, nonsense, and splice site variants, and small intragenic inserts and deletions. Typically, deletions of *TCF4* exons or the whole *TCF4* gene will not be detected by Sanger sequencing.

If a variant is not found by sequencing and a gene deletion is suspected, deletion/duplication analysis should be performed at the exon-level. Methods used include quantitative PCR and chromosome microarray analysis.

If a deletion is not found but Pitt-Hopkins syndrome is still suspected, karyotype analysis may be used to search for balanced translocations disrupting the coding region of *TCF4* (3, 9).

Genetic Counseling

Pitt-Hopkins syndrome is caused by a mutation in the *TCF4* gene, or a deletion of the chromosome region in which *TCF4* is located (18q21.2).

Most cases are caused by a *de novo* mutation (a new mutation, not present in either parent); cases of inheritance from a mosaic parent with a de novo mutation are exceedingly rare (10, 11).

Usually only one member of the family is affected. Parents are typically not affected, and although genetic testing could be offered, it would not be possible to entirely rule out a mutation because of somatic mosaicism (different cell lines may have different variants of *TCF4*).

Prenatal diagnosis and preimplantation genetic diagnosis are possible for pregnancies at increased risk of Pitt-Hopkins syndrome (e.g., if the parents have already had one affected child).

This risk of siblings being affected is low because the mutation is almost always *de novo* and not inherited. However, the risk is higher than that of the general population because of the possibility of mosaicism in parental germline cells (precursor cells of the egg or sperm).

For an individual with Pitt-Hopkins syndrome, the risk of passing on the syndrome to their offspring would be 50%. However, there are no known cases of individuals reproducing (2, 9).

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Version History

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