# PHOX2B gene

paired like homeobox 2B

## Normal Function

The *PHOX2B* gene provides instructions for making a protein that is important during development before birth. The PHOX2B protein helps support the formation of nerve cells (neurons) and regulates the process by which the neurons mature to carry out specific functions (differentiation). During neuron development, the protein is active in the neural crest, which is a group of cells in the early embryo that give rise to many tissues and organs. Neural crest cells migrate to form parts of the autonomic nervous system, which controls body functions such as breathing, blood pressure, heart rate, and digestion. Neural crest cells also give rise to many tissues in the face and skull, and other tissue and cell types.

The protein produced from the *PHOX2B* gene contains two areas where a protein building block (amino acid) called alanine is repeated multiple times. These stretches of alanines are known as polyalanine tracts or poly(A) tracts.

## Health Conditions Related to Genetic Changes

Congenital central hypoventilation syndrome

More than 75 mutations in the *PHOX2B* gene have been found to cause congenital central hypoventilation syndrome (CCHS). This condition is characterized by shallow breathing (hypoventilation), especially during sleep, that typically begins in infancy. Affected individuals often have other problems involving the autonomic nervous system, including difficulty regulating heart rate, blood pressure, and body temperature. Some people with CCHS also have abnormalities in the nerves that control the digestive tract ( Hirschsprung disease), resulting in severe constipation, intestinal blockage, and enlargement of the colon.

Most *PHOX2B* gene mutations that cause CCHS add extra alanines to the second polyalanine tract in the PHOX2B protein. This type of mutation is called a polyalanine repeat expansion. The mutations that cause CCHS typically increase the number of alanines from 20 to 25 or more. Other types of *PHOX2B* gene mutations have been identified in 8 to 10 percent of individuals with this disorder.

*PHOX2B* gene mutations that cause CCHS are believed to interfere with the PHOX2B

protein's role in supporting neuron formation and differentiation, especially in the autonomic nervous system. As a result, bodily functions that are controlled by this system, including regulation of breathing, heart rate, blood pressure, and body temperature, are inconsistent in CCHS.

Neuroblastoma

Several mutations in the *PHOX2B* gene have been identified in people with neuroblastoma, a type of cancerous tumor composed of immature neurons (neuroblasts) . Neuroblastoma and other cancers occur when a buildup of genetic mutations allow cells to grow and divide uncontrollably to form a tumor. In most cases, these genetic changes are acquired during a person's lifetime, called somatic mutations. Somatic mutations are present only in certain cells and are not inherited. Less commonly, gene mutations that increase the risk of developing cancer can be inherited from a parent. Both types of mutation occur in neuroblastoma. Somatic mutations in the *PHOX2B* gene increase the risk of developing sporadic neuroblastoma, and inherited mutations in the *PHOX2B* gene increase the risk of developing familial neuroblastoma.

In some people with neuroblastoma, mutations in the *PHOX2B* gene change a single protein building block (amino acid) in the PHOX2B protein. Other affected individuals may have an addition or deletion of several DNA building blocks (nucleotides) in the *PHOX2B* gene. Addition or deletion of nucleotides changes the sequence of amino acids in the PHOX2B protein. All of these types of mutations have been found in familial and sporadic neuroblastoma. The mutations are believed to interfere with the PHOX2B protein's role in supporting neuron differentiation, which results in an excess of immature neurons and leads to neuroblastoma.

Some people with *PHOX2B* gene mutations have both neuroblastoma and Hirschsprung disease. *PHOX2B* gene variations affect the autonomic nervous system and tissues that grow from the neural crest, resulting in an increased risk of developing both of these disorders.

## Other Names for This Gene

- NBLST2
- NBPhox
- neuroblastoma paired-type homeobox protein
- neuroblastoma Phox
- paired like homeobox 2b
- paired mesoderm homeobox 2b
- paired-like homeobox 2b
- Phox2b
- PHOX2B homeodomain protein
- PHX2B_HUMAN
- PMX2B

## Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PHOX2B (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=8929[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PHOX2B%5BTIAB%5D%29+OR+%28paired-like+homeobox+2b%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PAIRED-LIKE HOMEOBOX 2B; PHOX2B (https://omim.org/entry/603851)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/8929)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PHOX2B[gene])

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## Genomic Location

The *PHOX2B* gene is found on chromosome 4 (https://medlineplus.gov/genetics/chromosome/4/).

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