PAX3 gene

paired box 3

Normal Function

The *PAX3* gene belongs to a family of PAX genes that plays a critical role in the formation of tissues and organs during embryonic development. The PAX gene family is also important for maintaining the normal function of certain cells after birth. To carry out these roles, the PAX genes provide instructions for making proteins that attach (bind) to specific areas of DNA. By attaching to critical DNA regions, PAX proteins help control the activity of particular genes. On the basis of this action, PAX proteins are called transcription factors.

During embryonic development, the *PAX3* gene is active in cells called neural crest cells. These cells migrate from the developing spinal cord to specific regions in the embryo. The protein made from the *PAX3* gene directs the activity of other genes that signal neural crest cells to form specialized tissues or cell types such as some nerve tissue and pigment-producing cells called melanocytes. Melanocytes produce the pigment melanin, which contributes to hair, eye, and skin color. Melanocytes are also found in certain regions of the brain and inner ear.

Studies suggest that the PAX3 protein is also necessary for the normal development of bones in the face and skull (craniofacial bones) and elsewhere in the body, and for the formation of muscle tissue (myogenesis).

Health Conditions Related to Genetic Changes

Craniofacial-deafness-hand syndrome

At least one *PAX3* gene variant (also known as a mutation) has been identified in individuals with craniofacial-deafness-hand syndrome, a condition characterized by distinctive facial features, profound hearing loss, and abnormalities of the hand muscles that can restrict movement. The variant replaces a single protein building block (amino acid) called asparagine with another amino acid called lysine at position 47 in the PAX3 protein (written as Asn47Lys or N47K). This variant appears to affect the ability of the PAX3 protein to bind to DNA. As a result, the PAX3 protein cannot control the activity of other genes and cannot direct the neural crest cells to form specialized tissues. A lack of specialization of neural crest cells leads to the impaired growth of craniofacial bones, nerve tissue, and muscles seen in craniofacial-deafness-hand syndrome.

Waardenburg syndrome

PAX3 gene variants have been identified in people with Waardenburg syndrome, a group of genetic conditions that can cause hearing loss and changes in coloring (pigmentation) of the hair, skin, and eyes. Specifically, *PAX3* gene variants can cause Waardenburg syndrome types I and III.

Some of these variants change single amino acids in the PAX3 protein. Other variants lead to an abnormally small version of the PAX3 protein. Researchers believe that all *PAX3* gene variants have the same effect: they prevent the PAX3 protein from binding to DNA and regulating the activity of other genes. As a result, melanocytes do not develop in certain areas of the skin, hair, eyes, and inner ear, leading to hearing loss and the patchy loss of pigmentation that are characteristic features of Waardenburg syndrome. Additionally, loss of PAX3 protein function disrupts development of certain bones and muscles, producing abnormalities of the arms and hands in people with Waardenburg syndrome type III.

Cancers

Rearrangements of genetic material involving the *PAX3* gene are associated with a cancer of muscle tissue called alveolar rhabdomyosarcoma, which typically affects adolescents and young adults. This genetic change is somatic, which means that it is not inherited and occurs only in the cells that give rise to cancer. The rearrangements cause the *PAX3* gene to be fused with another gene, most commonly the *FOXO1A* gene (also called *FKHR*) on chromosome 13. The protein produced from the fused *PAX3-FOXO1A* gene has an increased ability to activate genes involved in myogenesis and can prevent cell death. As a result, muscle cell growth becomes uncontrolled, which can lead to this cancer of muscle tissue.

Somatic rearrangements involving the *PAX3* gene are also associated with a cancer of the nasal passages and sinuses called biphenotypic sinonasal sarcoma. This type of cancer usually occurs in adulthood and affects women more often than men. The genetic rearrangements involved in biphenotypic sinonasal sarcoma fuse the *PAX3* gene with another gene, most commonly the *MAML3* gene on chromosome 4. The protein produced from the fusion gene is overactive and turns on genes involved in the development of structures in the nasal passages and sinuses abnormally. As a result, cells in these structures can grow without control, forming a tumor.

Other Names for This Gene

- CDHS
- HUP2
- paired box gene 3 (Waardenburg syndrome 1)
- paired box homeotic gene 3
- paired domain gene 3
- paired domain gene HuP2
- PAX3/FKHR fusion gene

- PAX3_HUMAN
- WS1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PAX3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5077[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28PAX3%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- RHABDOMYOSARCOMA 2; RMS2 (https://omim.org/entry/268220)
- PAIRED BOX GENE 3; PAX3 (https://omim.org/entry/606597)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5077)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PAX3[gene])

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Genomic Location

The *PAX3* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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