ALX4 Gene

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ALX homeobox 4. The ALX4 gene provides instructions for making a member of the homeobox protein family.

genes

1. Normal Function

Homeobox proteins direct the formation of body structures during early embryonic development. The ALX4 protein is necessary for normal development of the skull and formation of the head and face, which begins early in fetal development. This protein is also involved in the formation of skin layers, but its role in this process is poorly understood.

The ALX4 protein is a transcription factor, which means that it attaches (binds) to DNA and controls the activity of certain genes. Specifically, the protein controls the activity of genes that regulate cell growth and division (proliferation), cell maturation and specialization (differentiation), cell movement (migration), and cell survival. The regulation of these functions ensures that cells start and stop growing at specific times and that they are positioned correctly during development.

2. Health Conditions Related to Genetic Changes

2.1. Enlarged parietal foramina

At least eight mutations in the *ALX4* gene have been found to cause enlarged parietal foramina type 2. This condition is characterized by enlarged openings (foramina) in the parietal bones, which are the two bones that form the top and sides of the skull. Openings in the parietal bones are normal during fetal development, but they usually close before birth. In people with this condition, the parietal foramina remain open throughout life.

The mutations that cause enlarged parietal foramina result in the production of an ALX4 protein that cannot bind to DNA, which alters the regulation of multiple genes. As a result, several cell processes are disrupted, including proliferation, differentiation, and survival. In early development, the skull seems to be particularly sensitive to changes in ALX4 protein activity. Specifically, cells in the skull that are involved in bone formation (ossification) cannot function normally, leading to a lack of bone in areas of the skull and resulting in enlarged parietal foramina.

2.2. Frontonasal dysplasia

At least four mutations in the *ALX4* gene have been found to cause frontonasal dysplasia. *ALX4* gene mutations cause a form of the disorder called frontonasal dysplasia type 2. In addition to facial malformations, this type can include features such as genital abnormalities in males, hair loss (alopecia), and enlarged parietal foramina (described above). The *ALX4* gene mutations that cause frontonasal dysplasia type 2 severely reduce or eliminate the function of the ALX4 protein. As a result, the protein cannot bind to DNA and regulate gene function, which leads to poorly controlled cell proliferation and migration during development. This abnormal cell growth and movement leads to malformations in the middle of the face, particularly affecting the nose, which leads to openings (clefts) in the nose. This abnormal development can also interfere with the proper formation of the skull, which likely contributes to enlarged parietal foramina. In some individuals, *ALX4* gene mutations impair the function of hair follicles and lead to alopecia, but the mechanism is unclear.

Because enlarged parietal foramina can be a feature of frontonasal dysplasia type 2 and because the two conditions are caused by mutations in the same gene, it is unclear whether these conditions are distinct disorders or part of a disease spectrum.

2.3. Potocki-Shaffer syndrome

A mutation resulting in the deletion of the *ALX4* gene causes a condition called Potocki-Shaffer syndrome. People with this condition have enlarged parietal foramina (described above) and multiple noncancerous bone tumors (osteochondromas). Other signs and symptoms seen in some people with Potocki-Shaffer syndrome include intellectual disability, developmental delay, distinctive facial features, vision problems, and defects in the heart, kidneys, and urinary tract.

Potocki-Shaffer syndrome (also called proximal 11p deletion syndrome) is caused by a deletion of genetic material from the short (p) arm of chromosome 11. In people with this condition, a loss of the *ALX4* gene within this region is responsible for enlarged parietal foramina. This feature occurs because a shortage of the *ALX4* transcription factor caused by deletion of the gene disrupts several cellular processes and impairs proper bone formation (ossification). The loss of additional genes in the deleted region likely contributes to the other features of Potocki-Shaffer syndrome. Specifically, loss of the *EXT2* gene results in multiple osteochondromas, and deletion of the *PHF21A* gene causes intellectual disability and distinctive facial features.

3. Other Names for This Gene

- ALX4_HUMAN
- FPP
- homeodomain transcription factor ALX4
- KIAA1788
- PFM
- PFM2

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