Periventricular heterotopia

Description

Periventricular heterotopia is a condition in which nerve cells (neurons) do not migrate properly during the early development of the fetal brain, from about the 6th week to the 24th week of pregnancy. Heterotopia means "out of place." In normal brain development, neurons form in the periventricular region, located around fluid-filled cavities (ventricles) near the center of the brain. The neurons then migrate outward to form the exterior of the brain (cerebral cortex) in six onion-like layers. In periventricular heterotopia, some neurons fail to migrate to their proper position and form clumps around the ventricles.

Periventricular heterotopia usually becomes evident when seizures first appear, often during the teenage years. The nodules around the ventricles are then typically discovered when magnetic resonance imaging (MRI) studies are done. Affected individuals usually have normal intelligence, although some have mild intellectual disability. Difficulty with reading and spelling (dyslexia) and movement problems have been reported in some people with periventricular heterotopia.

Less commonly, individuals with periventricular heterotopia may have other features including more severe brain malformations, small head size (microcephaly), developmental delays, recurrent infections, blood vessel abnormalities, stomach problems, or lung disease. Periventricular heterotopia may also occur in association with other conditions such as Ehlers-Danlos syndrome, which results in extremely flexible joints, skin that stretches easily, and fragile blood vessels.

Frequency

Periventricular heterotopia is a rare condition. Its incidence is unknown.

Causes

In most cases, periventricular heterotopia is caused by mutations in the *FLNA* gene. This gene provides instructions for producing the protein filamin A, which helps build the network of protein filaments (cytoskeleton) that gives structure to cells and allows them to change shape and move. Certain mutations in the *FLNA* gene result in an impaired FLNA protein that cannot perform this function, disrupting the normal migration patterns of neurons during brain development.

Periventricular heterotopia can also be caused by mutations in the *ARFGEF2* gene. This gene provides instructions for making a protein that is involved in the movement (trafficking) of small sac-like structures (vesicles) within the cell. Vesicle trafficking is important in controlling the migration of neurons during the development of the brain. Mutations in the *ARFGEF2* gene may disrupt this function, which could result in the abnormal neuronal migration seen in periventricular heterotopia.

Researchers believe that mutations in the *FLNA* or *ARFGEF2* genes may also result in weakening of the attachments (adhesion) between cells that form the lining of the ventricles. A weakened ventricular lining could allow some neurons to form clumps around the ventricles while others migrate normally to the exterior of the brain, as seen in periventricular heterotopia.

In a few cases, periventricular heterotopia has been associated with abnormalities in chromosome 5. In each case, the affected individual had extra genetic material caused by an abnormal duplication of part of this chromosome. It is not known how this duplicated genetic material results in the signs and symptoms of periventricular heterotopia.

Learn more about the genes and chromosome associated with Periventricular heterotopia

- ARFGEF2
- FLNA
- chromosome 5

Additional Information from NCBI Gene:

- NEDD4L

Inheritance

Periventricular heterotopia can have different inheritance patterns. When this condition is caused by mutations in the *FLNA* gene, it is inherited in an X-linked dominant pattern.

A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In X-linked periventricular heterotopia, males experience much more severe symptoms of the disorder than females, and in most cases die before birth.

In about 50 percent of cases of X-linked periventricular heterotopia, an affected person inherits the mutation from a mother who is also affected. Other cases may result from new mutations in the gene. These cases occur in people with no history of the disorder

in their family.

Periventricular heterotopia caused by mutations in the *ARFGEF2* gene is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Individuals with periventricular heterotopia in whom *ARFGEF2* gene mutations have been identified have a severe form of the disorder, including microcephaly, severe developmental delay, and seizures beginning in infancy. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

Other Names for This Condition

- Familial nodular heterotopia
- Periventricular nodular heterotopia

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Periventricular laminar heterotopia (https://www.ncbi.nlm.nih.gov/gtr/conditions/C2678104/)

Genetic and Rare Diseases Information Center

- Periventricular nodular heterotopia (https://rarediseases.info.nih.gov/diseases/12724/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Periventricular heterotopia%22)

Catalog of Genes and Diseases from OMIM

- PERIVENTRICULAR NODULAR HETEROTOPIA 1; PVNH1 (https://omim.org/entry/300049)
- PERIVENTRICULAR HETEROTOPIA WITH MICROCEPHALY, AUTOSOMAL RECESSIVE; ARPHM (https://omim.org/entry/608097)
- PERIVENTRICULAR NODULAR HETEROTOPIA 3; PVNH3 (https://omim.org/entry

/608098)

- PERIVENTRICULAR NODULAR HETEROTOPIA 7; PVNH7 (https://omim.org/entry/617201)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28periventricular+heterotopia%5BTIAB%5D%29+OR+%28periventricular+nodular+heterotopia%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

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