PAFAH1B1 Gene

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platelet activating factor acetylhydrolase 1b regulatory subunit 1

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1. Introduction

The *PAFAH1B1* gene (also known as *LIS1*) provides instructions for making a protein that is one part (subunit) of a complex called platelet activating factor acetyl hydrolase 1B (PAFAH1B). This complex regulates the amount of a molecule called platelet activating factor (PAF) in the brain. PAF is thought to be involved in directing the movement (migration) of nerve cells (neurons), a process known as neuronal migration. Proper neuronal migration is essential for normal brain development and function.

Separate from its role in the PAFAH1B complex, the PAFAH1B1 protein is also likely involved in the organization of the cell's structural framework (the cytoskeleton). This protein interacts with microtubules and regulates the activity of a variety of proteins that are involved in their function. Microtubules are rigid, hollow fibers that make up the cytoskeleton, and they are involved in cell division and movement

2. Health Conditions Related to Genetic Changes

2.1. Isolated lissencephaly sequence

At least 120 mutations in the *PAFAH1B1* gene have been found to cause isolated lissencephaly sequence (ILS). This condition is characterized by abnormal brain development that results in the brain having a smooth surface (lissencephaly) instead of its normal folds and grooves. Individuals with ILS have severe neurological problems, including severe intellectual disability and recurrent seizures (epilepsy) that begin in infancy. Most of the *PAFAH1B1* gene mutations that cause ILS lead to the production of an abnormally small, nonfunctional version of the PAFAH1B1 protein. *PAFAH1B1* gene mutations account for more than half of all ILS cases.

PAFAH1B1 gene mutations cause PAF levels to be reduced and impair the normal function of microtubules. As a result, neurons in the developing brain cannot migrate to their proper location, which impairs brain development and leads to the severe neurological problems characteristic of ILS.

2.2. Subcortical band heterotopia

At least seven mutations in the *PAFAH1B1* gene have been found to cause subcortical band heterotopia. This condition causes abnormal brain development that is less severe than ILS (described above). In people with subcortical band heterotopia, some neurons that should be part of a certain region of the brain do not reach their destination. The neurons stop their migration process in areas of the brain where they are not supposed to be and form band-like clusters of tissue. The signs and symptoms of subcortical band heterotopia can vary from severe intellectual disability and seizures that begin early in life to normal intelligence with mild seizures that occur later in life.

Most of these mutations change single amino acids in the PAFAH1B1 protein subunit. The abnormal PAFAH1B1 protein is less able to interact with microtubules and to attach (bind) to other subunits to form the PAFAH1B complex, both of which are needed for neuronal migration. Without proper neuronal migration, neurons in the developing brain can be misplaced, leading to the neurological problems in subcortical band heterotopia. *PAFAH1B1* gene mutations that cause subcortical band heterotopia are usually present in only some of the body's cells, a situation known as mosaicism. *PAFAH1B1* gene mutations that occur in all of the body's cells (germline mutations) usually cause isolated lissencephaly sequence (described above).

2.3. Miller-Dieker syndrome

A deletion of genetic material near the end of the short (p) arm of chromosome 17, that includes the *PAFAH1B1* gene, causes Miller-Dieker syndrome. This condition causes lissencephaly, intellectual disability, seizures, distinctive facial features, and other signs and symptoms.

As a result of the deletion, people with this condition have only one copy of the *PAFAH1B1* gene in each cell instead of the usual two copies. A deletion of one copy of the *PAFAH1B1* gene in each cell reduces the amount of PAFAH1B1 protein by about half. Researchers believe that a shortage of this protein is responsible for many of the features of Miller-Dieker syndrome, primarily lissencephaly, intellectual disability, and seizures.

Other genes deleted in the same region of chromosome 17 are likely responsible for the other features of Miller-Dieker syndrome.

More About This Health Condition

Other Names for This Gene

- LIS1
- LIS1_HUMAN
- LIS2
- lissencephaly 1 protein
- MDCR
- platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (45kDa)
- platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit
- platelet-activating factor acetylhydrolase, isoform Ib, subunit 1 (45kDa)

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