PNPLA6 gene

patatin like phospholipase domain containing 6

Normal Function

The *PNPLA6* gene provides instructions for making a protein called neuropathy target esterase (NTE). The NTE protein is involved in the breakdown of certain fats (lipids). Specifically, NTE breaks down a lipid called lysophosphatidylcholine, which is one of several compounds found in the outer membranes surrounding cells. The correct levels of these compounds are critical to the stability of the cell membranes.

The NTE protein is found most abundantly in the nervous system. It plays an important role in maintaining the stability of the membranes surrounding nerve cells (neurons) and of these cells' specialized extensions, called axons, that transmit nerve impulses. NTE may also play a role in the release of hormones from the pituitary gland, a process that requires particular changes in the cell membrane and appears to involve the lipids found there. The pituitary gland is located at the base of the brain and produces several hormones, including those that help direct sexual development and growth.

Health Conditions Related to Genetic Changes

Boucher-Neuhäuser syndrome

More than a dozen mutations in the *PNPLA6* gene have been found to cause Boucher-Neuhäuser syndrome, a disorder characterized by coordination and balance problems (ataxia), vision impairment, and delayed puberty. The mutations are thought to impair the function of the NTE protein. Researchers are unsure how such a reduction in function leads to the signs and symptoms of the condition. They speculate that impairment of lysophosphatidylcholine metabolism alters the balance of compounds in the cell membrane. This imbalance may damage axons, leading to the movement and vision problems that characterize Boucher-Neuhäuser syndrome. The imbalance is also thought to impair the release of hormones involved in sexual development, accounting for the delayed puberty in affected individuals.

Gordon Holmes syndrome

At least six mutations in the *PNPLA6* gene cause Gordon Holmes syndrome, a rare condition characterized by ataxia and reduced production of hormones that direct sexual development (hypogonadotropic hypogonadism), which leads to delayed or

absent puberty or other reproductive problems. As in Boucher-Neuhäuser syndrome (described above), the mutations that cause Gordon Holmes syndrome impair the function of the NTE protein, which researchers suspect disrupts the levels of lysophosphatidylcholine in cell membranes. The resulting imbalance of compounds in cell membranes is thought to damage neurons in the brain, causing ataxia, and impair the pituitary gland's release of hormones involved in sexual development, leading to hypogonadotropic hypogonadism. It is unclear how mutations in the same gene cause different combinations of features.

Other disorders

Mutations in the *PNPLA6* gene cause a continuous spectrum of neurological conditions called *PNPLA6*-related disorders. Conditions in this group include Boucher-Neuhäuser syndrome (described above), Gordon Holmes syndrome (described above), Oliver-McFarlane syndrome, Laurence-Moon syndrome, and spastic paraplegia type 39. *PNPLA6*-related disorders feature combinations of overlapping signs and symptoms, including ataxia, muscle stiffness (spasticity), abnormally fast (brisk) reflexes, reduced sensation in the extremities (peripheral neuropathy), intellectual disability or other cognitive problems, eye abnormalities, impaired vision, hair abnormalities, hypogonadotropic hypogonadism, and reduced function of the pituitary gland (hypopituitarism). It is unknown how mutations in a single gene cause such a wide range of disorders.

Other Names for This Gene

- BNHS
- iPLA2delta
- LNMS
- NTE
- NTEMND
- OMCS
- patatin-like phospholipase domain-containing protein 6
- SPG39
- sws

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PNPLA6 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=10908[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PNPLA6%5BTIAB%5D%

29+OR+%28patatin+like+phospholipase+domain+containing+6%5BTIAB%5D%29%29+OR+%28%28NTE%5BTIAB%5D%29+OR+%28patatin-like+phospholipase+domain-containing+protein+6%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+NOT+%28non-targeted+effects%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PATATIN-LIKE PHOSPHOLIPASE DOMAIN-CONTAINING PROTEIN 6; PNPLA6 (https://omim.org/entry/603197)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/10908)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PNPLA6[gene])

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Genomic Location

The *PNPLA6* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

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