PAH gene

phenylalanine hydroxylase

Normal Function

The *PAH* gene provides instructions for making an enzyme called phenylalanine hydroxylase. This enzyme helps process phenylalanine, which is a building block of proteins (amino acid). Phenylalanine is obtained through the diet; it is found in certain foods (such as meat, eggs, nuts, and milk) and in some artificial sweeteners.

Phenylalanine hydroxylase is responsible for the conversion of phenylalanine to another amino acid, tyrosine. The enzyme works with a molecule called tetrahydrobiopterin (BH4) to carry out this chemical reaction. Tyrosine is used to make several types of hormones and a pigment called melanin, which gives hair and skin their color. It is also used to make neurotransmitters, which are chemicals that transmit signals in the brain. Tyrosine can also be broken down into smaller molecules that are used to produce energy.

Health Conditions Related to Genetic Changes

Phenylketonuria

Hundreds of variants (also called mutations) in the *PAH* gene have been identified in people with phenylketonuria (PKU). This condition increase the levels of phenylalanine in the blood. If PKU is not treated, phenylalanine can build up to harmful levels, causing intellectual disability and other serious health problems.

Most of the variants that cause PKU change single amino acids in phenylalanine hydroxylase. For example, the most common variant in many populations replaces the amino acid arginine with the amino acid tryptophan at position 408 (written as Arg408Trp or R408W) in phenylalanine hydroxylase. Other *PAH* gene variants delete small amounts of DNA from the gene or disrupt the way the gene's instructions are used to make phenylalanine hydroxylase.

PAH gene variants reduce the activity of phenylalanine hydroxylase, preventing it from processing phenylalanine effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.

Classic PKU, the most severe form of the disorder, occurs in people who have very low levels of phenylalanine hydroxylase activity or who have no phenylalanine hydroxylase activity at all. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems. Variants in the *PAH* gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

Other Names for This Gene

- L-Phenylalanine,tetrahydrobiopterin:oxygen oxidoreductase (4-hydroxylating)
- PH4H_HUMAN
- Phenylalaninase
- Phenylalanine 4-Hydroxylase
- Phenylalanine 4-Monooxygenase
- PKU1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PAH (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5053[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=((PAH%5BTI%5D)+OR+(phenylalanine+hydroxylase%5BMAJR%5D)+OR+(phenylalanine+hydroxylase%5BTI%5D))+OR+((phenylalanine+4-hydroxylase%5BTIAB%5D)+OR+(phenylalanine+4-monooxygenase%5BTIAB%5D))+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+5000+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PHENYLALANINE HYDROXYLASE; PAH (https://omim.org/entry/612349)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5053)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PAH[gene])

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Genomic Location

The *PAH* gene is found on chromosome 12 (https://medlineplus.gov/genetics/chromosome/12/).

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