PAH gene

phenylalanine hydroxylase

Normal Function

The *PAH* gene provides instructions for making an enzyme called phenylalanine hydroxylase. This enzyme is responsible for the first step in processing phenylalanine, which is a building block of proteins (an amino acid) obtained through the diet. Phenylalanine is found in all proteins 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, certain chemicals that transmit signals in the brain (neurotransmitters), and a pigment called melanin, which gives hair and skin their color. Tyrosine can also be broken down into smaller molecules that are used to produce energy.

Health Conditions Related to Genetic Changes

phenylketonuria

More than 500 mutations in the *PAH* gene have been identified in people with phenylketonuria (PKU). Most of these mutations change single amino acids in phenylalanine hydroxylase. For example, the most common mutation in many populations replaces the amino acid arginine with the amino acid tryptophan at position 408 (written as Arg408Trp or R408W). Other *PAH* mutations delete small amounts of DNA from the gene or disrupt the way the gene's instructions are used to make phenylalanine hydroxylase.

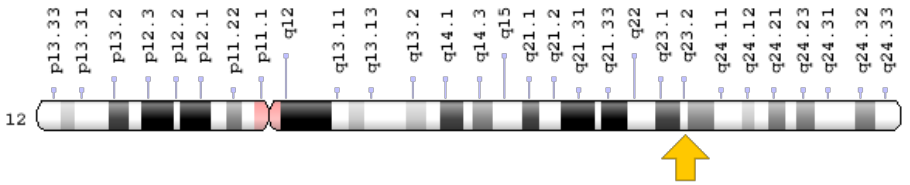
PAH mutations reduce the activity of phenylalanine hydroxylase, preventing it from processing phenylalanine effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive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

Classic PKU, the most severe form of the disorder, occurs when phenylalanine hydroxylase activity is severely reduced or absent. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems. Mutations 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.

Chromosomal Location

Cytogenetic Location: 12q23.2, which is the long (q) arm of chromosome 12 at position 23.2

Molecular Location: base pairs 102,838,326 to 102,917,603 on chromosome 12 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

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

Educational Resources

- Basic Neurochemistry (sixth edition, 1999): Phenylalanine Metabolism: Phenylketonuria
  https://www.ncbi.nlm.nih.gov/books/NBK28101/

GeneReviews

- Phenylalanine Hydroxylase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK1504

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28PAH%5BTI%5D%29+OR+%28phenylalanine+hydroxylase%5BMAJR%5D%29+OR+%28phenylalanine+hydroxylase%5BTI%5D%29%29+OR+%28%28phenylalanine+4-hydroxylase%5BTIAB%5D%29+OR+%28phenylalanine+4-monooxygenase%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- PHENYLALANINE HYDROXYLASE
  http://omim.org/entry/612349

Research Resources

- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=PAH%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=8582
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/5053
- PAHdb Phenylalanine Hydroxylase Locus Knowledgebase
  http://www.pahdb.mcgill.ca/
- UniProt
  http://www.uniprot.org/uniprot/P00439

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