MTHFR gene

methylenetetrahydrofolate reductase

Normal Function

The *MTHFR* gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

Health Conditions Related to Genetic Changes

Homocystinuria

At least 40 mutations in the *MTHFR* gene have been identified in people with homocystinuria, a disorder in which the body is unable to process homocysteine and methionine properly. People with this condition often develop eye problems, abnormal blood clotting, skeletal abnormalities, and cognitive problems. Most of the mutations that cause homocystinuria change single amino acids in methylenetetrahydrofolate reductase. These changes impair the function of the enzyme, and some cause the enzyme to be turned off (inactivated). Other mutations lead to the production of an abnormally small, nonfunctional version of the enzyme. Without functional methylenetetrahydrofolate reductase, homocysteine cannot be converted to methionine. As a result, homocysteine builds up in the bloodstream, and the amount of methionine is reduced. Some of the excess homocysteine is excreted in urine (homocystinuria). Researchers have not determined how altered levels of homocysteine and methionine lead to the various health problems affecting multiple parts of the body in people with homocystinuria.

Age-related hearing loss

Anencephaly

Several variations (polymorphisms) in the *MTHFR* gene have been associated with an increased risk of neural tube defects, a group of birth defects that occur during the development of the brain and spinal cord. Anencephaly is one of the most common types of neural tube defect. Affected individuals are missing large parts of the brain and have missing or incompletely formed skull bones.

The most well-studied polymorphism related to neural tube defects changes a single DNA building block (nucleotide) in the *MTHFR* gene. Specifically, it replaces the nucleotide cytosine with the nucleotide thymine at position 677 (written as 677C>T). This common variant results in a form of methylenetetrahydrofolate reductase that has reduced activity at higher temperatures (thermolabile). People with the 677C>T polymorphism, particularly those with two copies of the genetic change, have elevated levels of homocysteine in their blood resulting from the reduced activity of methylenetetrahydrofolate reductase.

Researchers have studied *MTHFR* gene polymorphisms in individuals with neural tube defects and in their mothers, but it remains unclear how these variations could affect the developing brain and spinal cord. The increased risk of neural tube defects may be related to differences in the ability of methylenetetrahydrofolate reductase to process folate; a shortage of this vitamin is an established risk factor for neural tube defects.

Although *MTHFR* gene polymorphisms are associated with an increased risk of neural tube defects, these variations are common in many populations worldwide. Most people with *MTHFR* gene polymorphisms do not have neural tube defects, and their children are also typically unaffected. Changes in the *MTHFR* gene are only one of many genetic and environmental factors that are thought to contribute to these complex conditions.

Spina bifida

Polymorphisms in the *MTHFR* gene are also associated with an increased risk of spina bifida, another common type of neural tube defect. In people with this condition, when the spine forms, the bones of the spinal column do not close completely around the developing nerves of the spinal cord. As a result, part of the spinal cord may protrude through an opening in the spine, leading to permanent nerve damage.

As described above, variations in the *MTHFR* gene may increase the risk of neural tube defects by changing the ability of methylenetetrahydrofolate reductase to process folate. However, these variations are common in many populations worldwide. Most people with *MTHFR* gene polymorphisms do not have neural tube defects, nor do their children.

Other disorders

Polymorphisms in the *MTHFR* gene have also been studied as possible risk factors for a variety of common conditions. These include heart disease, stroke, high blood pressure (hypertension), high blood pressure during pregnancy (preeclampsia), an eye disorder called glaucoma, psychiatric disorders, and certain types of cancer. Research indicates that individuals who have the 677C>T polymorphism on both copies of the *MTHFR* gene have an increased risk of developing vascular disease, including heart disease and stroke. The 677C>T polymorphism has also been suggested as a risk factor for cleft lip and palate, a birth defect in which there is a split in the upper lip and an opening in the roof of the mouth. Many of the *MTHFR* gene

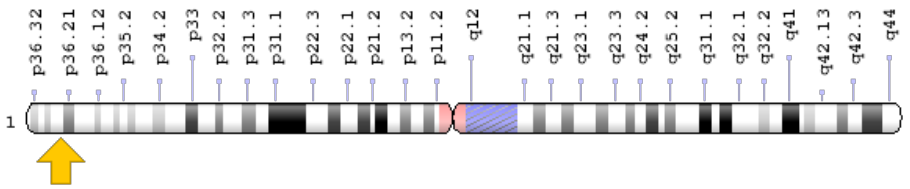
polymorphisms alter or decrease the activity of methylenetetrahydrofolate reductase, leading to an increase of homocysteine in the blood. This increase in homocysteine levels may contribute to the development of many of these conditions.

Studies of *MTHFR* gene variations in people with these disorders have had mixed results, with associations found in some studies but not in others. Therefore, it remains unclear what role changes in the *MTHFR* gene play in these disorders. It is likely that additional factors influence the processing of homocysteine and that variations in homocysteine levels play a role in whether a person develops any of these conditions. A large number of genetic and environmental factors, most of which remain unknown, likely determine the risk of developing most common, complex conditions.

Chromosomal Location

Cytogenetic Location: 1p36.22, which is the short (p) arm of chromosome 1 at position 36.22

Molecular Location: base pairs 11,785,730 to 11,806,103 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- 5,10-methylenetetrahydrofolate reductase
- 5,10-methylenetetrahydrofolate reductase (NADPH)
- methylenetetrahydrofolate reductase (NAD(P)H)
- MTHR_HUMAN

Additional Information & Resources

Educational Resources

- Madame Curie Bioscience Database: Molecular Biology of Methylenetetrahydrofolate Reductase (MTHFR) and Overview of Mutations/ Polymorphisms
  https://www.ncbi.nlm.nih.gov/books/NBK6561/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28MTHFR%5BTI%5D%29+OR+%285,10-methylenetetrahydrofolate+reductase%5BTI%5D%29%29+AND+%28%285,10-methylenetetrahydrofolate+reductase+%28nadph%29%29+OR+%28methylene-thf+reductase+%28nadph%29%29+OR+%28methylenetetrahydrofolate+reductase+%28nadph2%29%29+OR+%28methylene+tetrahydrofolate+reductase%5BMAJR%5D%29+OR+%28methylenetetrahydrofolate+reductase%5BMAJR%5D%29+OR+%28methylenetetrahydrofolate+reductase+%28nadph%29%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE
  http://omim.org/entry/607093

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/MTHFRID41448ch1p36.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MTHFR%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7436
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4524
- UniProt
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