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. Methylene tetrahydrofolate reductase is important for a chemical reaction involving the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a form of folate called 5,10-methylenetetrahydrofolate to a different form of folate called 5-methyltetrahydrofolate. This is the primary form of folate found in blood, and is necessary 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 learning 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**

**Alopecia areata**

**Anencephaly**

Some studies have found that variations (polymorphisms) in the *MTHFR* gene have been associated with a small 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 MTHFR polymorphism 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 (the enzyme is thermolabile). People with the 677C>T polymorphism, particularly those with the genetic change in both copies of the gene, have elevated levels of homocysteine in their blood (hyperhomocysteinemia) resulting from the reduced activity of methylenetetrahydrofolate reductase.

Researchers have studied MTHFR gene polymorphisms and hyperhomocysteinemia in individuals with neural tube defects and in their mothers, but it remains unclear how these variations affect the developing brain and spinal cord. The association with neural tube defects may be related to differences in the ability of methylenetetrahydrofolate reductase to process folate. While a shortage (deficiency) of this vitamin is an established risk factor for neural tube defects, there are many factors that can contribute to folate deficiency.

MTHFR gene polymorphisms are common worldwide, with an estimated 25 percent of Hispanics and 10 to 15 percent of North American whites having the 677C>T polymorphism in both copies of the gene. Most people with MTHFR gene polymorphisms do not have neural tube defects, and their children are also typically unaffected.

**Spina bifida**

Some studies have found that polymorphisms in the MTHFR gene are also associated with a small increased risk of spina bifida, another common type of neural tube defect. When the spine forms in people with this condition, 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 stick out through an opening in the spine, leading to permanent nerve damage.

As described above, variations in the MTHFR gene generally result in hyperhomocysteinemia due to reduced activity of methylenetetrahydrofolate reductase and its ability to process folate. It is unclear how MTHFR gene changes might influence the development of neural tube defects. 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 can alter or decrease the activity of methylenetetrahydrofolate reductase, leading to a mild increase of homocysteine in the blood (hyperhomocysteinemia). The two MTHFR gene polymorphisms that are the most common and the most frequently studied are 677C>T and a change
that replaces the nucleotide adenosine with the nucleotide cytosine at position 1298 (written as 1298A>C).

An increase in homocysteine levels caused by MTHFR gene polymorphisms have been studied as possible risk factors for a variety of common conditions. These include high blood pressure (hypertension), blood clots, pregnancy loss, 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.

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, the role that changes in the MTHFR gene play in these disorders remains unclear. 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 11,785,723 to 11,806,103 on chromosome 1 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (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/

• Medical Genetics Summaries from the National Center for Biotechnology Information: Methylene tetrahydrofolate Reductase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK66131/

• MedlinePlus Medical Tests: MTHFR Mutation Test
  https://medlineplus.gov/lab-tests/mthfr-mutation-test/

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+nadph%29+OR+%28methylene-thf+reductase+nadph%29+OR+%28methylenetetrahydrofolate+reductase+nadph2%29+OR+%28methylene+tetrahydrofolate+reductase%5BMAJR%5D%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+1080+days%22%5Bdp%5D

Catalog of Genes and Diseases from 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

• Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:4524
• NCBI Gene

• UniProt
https://www.uniprot.org/uniprot/P42898

Sources for This Summary

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