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 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

MedlinePlus Genetics provides information about Age-related hearing loss

Alopecia areata

MedlinePlus Genetics provides information about 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 reduce 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.

Other Names for This Gene

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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MTHFR (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4524[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?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+OR+%28meth

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Catalog of Genes and Diseases from OMIM

- 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE; MTHFR (https://omim.org/entry/607093)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/4524)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=MTHFR[gene])

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Genomic Location

The *MTHFR* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

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