

## Gene Section

### Mini Review

# MTHFR (5,10-Methylenetetrahydrofolate reductase)

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## Identity

**Other names:** MTR; MTHR

**HGNC (Hugo):** MTHFR

**Location:** 1p36.22

## DNA/RNA

### Description

The gene encompasses 19.3 kb of DNA; 11 exons.

### Transcription

For MTHFR, transcripts of 9.0, 7.2, 6.3, 3.0 and 2.8 kb were observed. The different-sized transcripts result from alternate transcription start sites and

multiple polyadenylation signals. The total abundance is low, and the proportion of each transcript differs among tissues.

## Protein

### Description

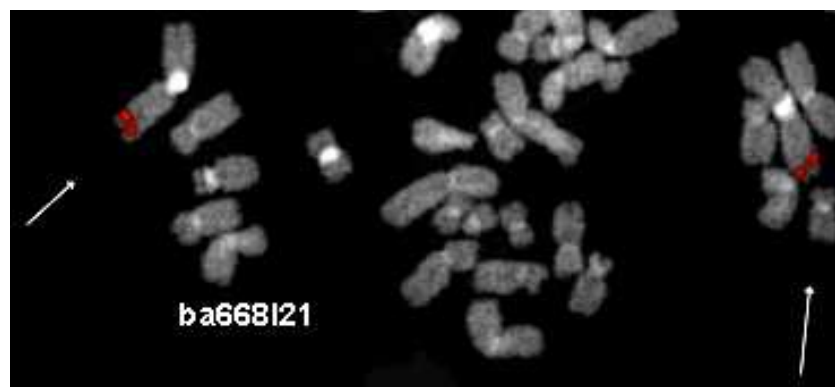
656 amino acids; 74.6 kDa protein.

### Expression

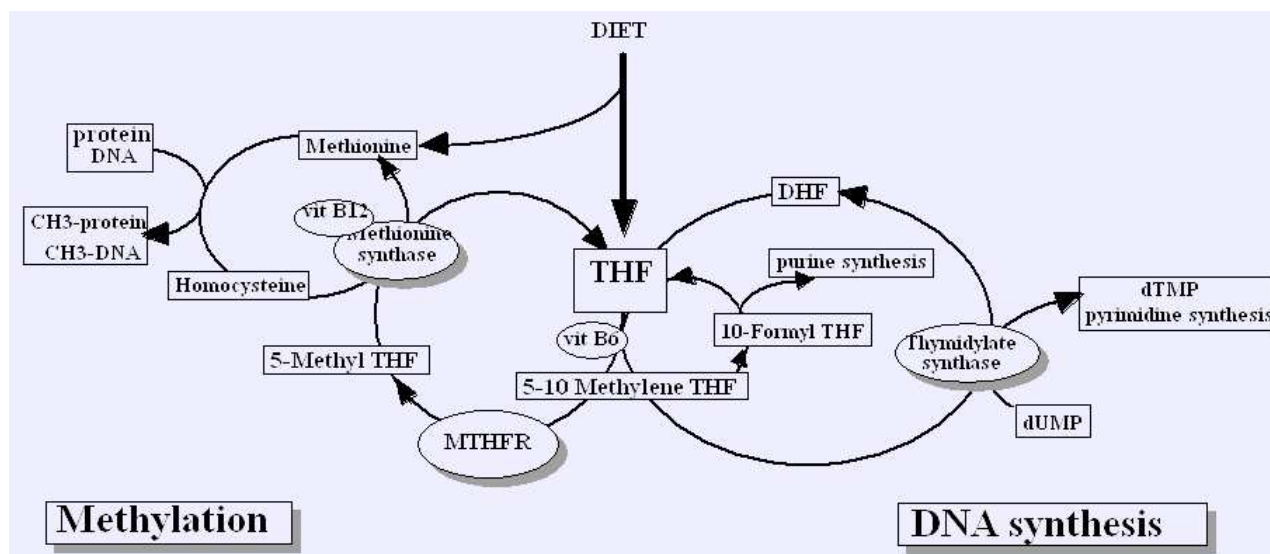
Expression is more intense in testis, intermediate in brain and kidney, and lower in other tissues.

### Localisation

Cytosolic.



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.



MTHFR metabolic pathway

### Function

MTHFR catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for homocysteine remethylation to methionine.

### Homology

FAD-linked oxidoreductase.

## Mutations

### Germinal

Two common polymorphisms 677C-T and 1298A-C have been identified. These polymorphisms are responsible for the synthesis of a thermolabile form of MTHFR. The 677TT genotype was particularly common in northern China (20%), southern Italy (26%), and Mexico (32%). The 677C>T mutation in the MTHFR gene is an important cause of mild hyperhomocysteinaemia. The second polymorphism at nucleotide position 1298 is not as well characterized.

## Implicated in

### Homocystinuria due to deficiency of methylenetetrahydrofolate reductase activity

#### Disease

This form of homocystinuria is caused by mutation in the 5, 10-alpha-methylenetetrahydrofolate reductase gene. This homocystinuria is autosomal recessive and shows a wide range of clinical symptoms, such as developmental delay, severe mental retardation, perinatal death, psychiatric disturbances, and later-onset neurodegenerative disorders. In the classic form, both thermostable and thermolabile enzyme variants have been identified.

### Cancer

#### Disease

In some cancers, folate and other nutrients involved in the MTHFR metabolic pathway appear to interact with MTHFR polymorphisms to further modify cancer risk. In most studies, MTHFR 677TT and 1298CC are associated with moderately reduced colorectal cancer risk, in particular in individuals who had higher folate levels. In individuals with low folate intake and/or high alcohol consumption, cancer risk may be increased. Moreover, both adults and children with the variant forms of MTHFR seems to have a decreased risk of lymphoid leukemias. MTHFR polymorphisms were also associated with other cancers as breast, head and neck, liver, gastric or lung cancers.

#### Oncogenesis

Reduction of 5, 10-methylenetetrahydrofolate (methyleneTHF), a donor for methylating dUMP to dTMP in DNA synthesis, to 5-methyltetrahydrofolate (methylTHF), the primary methyl donor for methionine synthesis, is catalyzed by MTHFR. Diminution in the activity of the MTHFR enzyme increases the pool of methyleneTHF at the expense of the pool of methylTHF. Enhanced availability of methyleneTHF in the DNA synthesis pathway reduces misincorporation of uracil into DNA, which might otherwise result in double-strand breaks during uracil excision repair processes, thus increasing the risk of chromosomal aberrations. Moreover, the MTHFR polymorphisms influences DNA methylation status through interaction with folate status.

### Coronary Artery Disease

#### Disease

The 677TT MTHFR allele was correlated with coronary artery disease. However, the role of this

polymorphism in the causation of coronary artery disease is controversial.

## Depression

### Disease

Hyperhomocysteinemia and the 677TT genotype were significantly related to depression.

## To be noted

### Note

MTHFR polymorphisms influence the metabolism of folates and could modify the pharmacodynamics of antifolates and many other drugs whose metabolism, biochemical effects, or target structures require methylation reactions.

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