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Gene test information

MTHFR 677T UND METHOTREXATE TOXICITY

- **Background**

  Methotrexate is an antimetabolite drug used in treatment of cancer and autoimmune diseases. As a structural analogue of folate, methotrexate interferes with folate metabolism by inhibiting dihydrofolate reductase, which leads to depletion of cellular folate. Supplementation with folate or folinic acid (leucovorin) reduces the efficacy and toxicity of methotrexate.

  MTHFR is an important enzyme in maintaining cellular folate pools, and MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia may affect methotrexate sensitivity and contribute to toxicity.

  A common MTHFR mutations, 677C>T, results in reduced MTHFR enzymatic activity. Heterozygous carriers of a 677T variant have approximately 60 percent of normal MTHFR enzyme normal activity. Homozygotes for 677T have about 30 percent of MTHFR enzyme activity. Carriage of MTHFR 677T variants has been associated with increased risk for methotrexate toxicities.

- **MTHFR genotypes**

Genotype	Frequency	Commentary
MTHFR 677 CC :	41%	Wild-type ("normal") genotype. No MTHFR 677T allele detected.
MTHFR 677 CT :	47%	Heterozygous carrier of a MTHFR 677T allele. Modestly increased risk for methotrexate toxicity
MTHFR 677 TT :	12%	Homozygous carrier of two MTHFR 677T alleles. Increased risk for methotrexate toxicity

- **Indications for testing**

  Estimation of individual risk for methotrexate toxicity

References:

Hider SL et al. The pharmacogenetics of methotrexate. Rheumatology 2007;46:1520-4.

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