KASHI CLINICAL LABORATORIES

MTHFR
Genotyping Panel

PATIENT
PFirst PLast
DOB: 01/01/72

ORDERING PROVIDER
Example Organization

LABORATORY INFORMATION

Lab ID:	N8C9841
Collection Date:	01/11/10
Test Date:	01/21/10
Report Date:	01/22/10

MTHFR C677T CT
MTHFR A1298C CA
This patient's genotype is compound heterozygous for MTHFR. There is 48% enzyme activity. Supporting optimal methylation with folate and hydroxy- or methyl-cobalamin may be warranted. There is potential for decreased methotrexate tolerance. Every individual has a variable need for folate and dosing should be adjusted based on symptoms.

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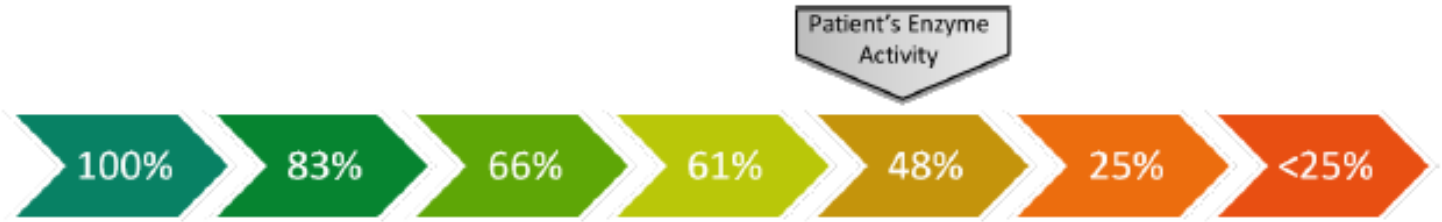
Test	Genotype	Result
C677T Mutation	C/T	Positive
A1298C Mutation	C/A	Positive

PATIENT'S APPROXIMATE MTHFR ENZYME ACTIVITY[1]



MTHFR GENOTYPE SUMMARY

This patient carries ONE C677T gene mutation and ONE A1298C gene mutation.

- Patient exhibits heterozygosity for both the C677T gene mutation and the A1298C gene mutation. This is referred to as a compound heterozygote.
- Compound heterozygosity is associated with intermediate enzyme activity.
- The patient's genotypes should be interpreted in light of clinical information.
- Possible increased sensitivity to Methotrexate leading to lower dosage requirements, increased side effects or intolerance of the drug.

MTHFR BACKGROUND INFORMATION

The MTHFR (methylenetetrahydrofolate reductase) gene produces an enzyme that helps in processing folate and regulating homocysteine levels in the body. Folate is a critical nutrient involved in methylation, DNA synthesis and amino acid metabolism.[2]

Impaired folate metabolism due to MTHFR enzyme inactivity, or a low folate level, results in elevated plasma homocysteine.[3] Homocysteine is an amino acid synthesized by the body through demethylation of methionine. In the presence of adequate B vitamins, homocysteine is either irreversibly degraded to cysteine or it is re-methylated back to methionine, an essential amino acid.[4] An elevated homocysteine level is known to be an independent risk factor for ischemic stroke, thrombotic and cardiovascular diseases.[5,6] Folate, vitamin B6 or vitamin B12 are all necessary for the proper conversion of homocysteine into methionine. A deficiency in any of these vitamins can cause homocysteine levels to rise.

Two single nucleotide variants known to affect MTHFR function are C677T (a change from cytosine to thymine at position 677 within the gene) and the A1298C mutation (a change from adenine to cytosine at position 1298 within the gene).[1,6,7] It is not uncommon for some individuals to have both MTHFR variants. Clinical relevance for hyperhomocysteniemia is associated with homozygosity for the C677T variant allele. In general, these genotypes produce MTHFR enzyme with reduced function and activity.

In addition to vascular health, defects in folate metabolism due to dietary factors or MTHFR mutations may contribute to the pathophysiology of neural tube defects and a variety of malignancies.[1,8] Also, a strong association between MTHFR variants and methotrexate toxicity has been reported.[9] Methotrexate, a drug used in treatment of cancer and autoimmune diseases, is a

structural analogue of folate that interferes with folate metabolism and leads to depletion of cellular folate. MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia may affect methotrexate sensitivity and contribute to toxicity.[9] MTHFR genotyping may support methotrexate dose adjustment and limitation / discontinuation of therapy in affected individuals.

MTHFR: BEHAVIORAL HEALTH INFORMATION

Impaired folate metabolism due to reduced MTHFR enzyme activity, or decreased folate, results in elevated plasma homocysteine which has been linked to depression.[5,10,11] There is no evidence to suggest that the A1298C mutation alone affects plasma homocysteine levels, however, it has been demonstrated that individuals who are compound heterozygotes for both the C677T and the A1298C mutations may have increased plasma homocysteine concentrations.[1] Elevated homocysteine levels are inversely associated with memory score[12] , and directly related to brain atrophy[13] and depressive symptoms.[5,10]

Folate levels are directly related to memory scores,[12] and inversely related to depressive symptoms in women.[11] C677T T/T homozygous allele carriers are associated with a higher risk of depression, schizophrenia, and bipolar disorder as compared to the C/C genotype.[5,14,15] Depressed, schizophrenic, and bipolar individuals showed a trend towards increased frequency of the T allele, therefore C/T heterozygous allele carriers may have an intermediate risk for depression.[14,15] A1298C C/C homozygous allele carriers are reported to have an increased risk of depression and schizophrenia compared to homozygous A/A carriers, while A/C heterozygous allele carriers did not show an increased risk.[14]

MTHFR: CARDIAC HEALTH INFORMATION

An elevated homocysteine level has been identified as an independent risk factor for ischemic stroke, thrombotic and cardiovascular diseases.[5,6,16] However, it is important to remember that this is a multifactorial condition, involving a combination of genetic, physiologic, and environmental factors, and clinical relevance of MTHFR testing should be interpreted in light of clinical information.

Testing Limitations: A very rare allele near the A1298C location can result in a false positive for the presence of the "C" SNP. Our testing method does not screen for this allele owing to its exceedingly rare occurrence. If reports obtained do not match the clinical findings, additional testing should be considered. All results should be interpreted in the context of clinical findings, relevant history, and other laboratory findings.

This test detects only specific targeted genetic variations and there is a possibility that other genetic variants not detected by this test may be present. The DNA variants tested for in this report have been scientifically determined to be possible risk factors for the reported condition. The content of this report is provided for informational purposes only, not as a diagnostic tool. The report does not supersede the judgment of a qualified medical provider. This test is not a substitute for a comprehensive consideration of all factors that influence the maintenance of a healthy body. Genetic risk factors are not guarantees that you will develop a condition, and in many cases, the presence of a particular DNA variant may only play a minor role in your risk for disease, compared with environmental and lifestyle factors. This test is not FDA approved. The test's performance characteristics have been established and maintained by Kashi Clinical Laboratories under CLIA and CAP compliance.

Reported and Reviewed By:

Zahra Mehdizadeh Kashi, Ph.D., HCLD
CEO and Laboratory Director

MTHFR TREATMENT OPTIONS

The following supplements may benefit a patient's folate metabolism pathway.

	Supplement	Starting Dosage Range	Notes
✓	L-5-MTHF or L-5-FTHF	400 mcg – 15 mg	Using an active form of folate is crucial when the patient's ability to generate active folate is compromised.
✓	Methylcobalamin (B12)	500 mcg (sublingual preferred)	Using the active form of Vitamin B12 ensures the patient has the necessary methyl groups to regenerate the active folate.
✓	Active B Complex	10-25 mg Pyridoxal-5'-phosphate (B6) 2.1 mg Riboflavin-5'-phosphate (B2)	An active B complex will supply the patient with the other necessary cofactors to support the generation of active folate.

OPTIONAL DEPENDING ON HEALTH CONDITIONS AND PROVIDER DISCRETION

- Betaine/Trimethylglycine (TMG): TMG is very useful in patients with elevated homocysteine levels.
- N-Acetyl Cysteine (NAC): NAC assists with liberation of homocysteine from its receptors and helps to reduce oxidation.

Notice: *This information does not take into consideration patient health history, interaction with other medications or supplements, and/or allergies. It is the responsibility of the physician to determine appropriate dosing choices based on all clinical data.*

RECOMMENDED INTERVENTIONS

Lifestyle interventions:

- Avoid alcohol. Mutation carriers that consume high levels of alcohol show low levels of plasma folate and higher levels of homocysteine.[17]
- Avoid smoking. Smoking has been shown to elevate homocysteine levels.[17]

Folate:

Folate rich diet:

- Eating a folate rich diet provides greater amounts of substrate for the enzyme. Aiming for 400 mcg daily from various sources is recommended for most individuals, 600-800 mcg daily should be consumed by pregnant women.[18,19] Sources include: liver, dark leafy green vegetables, fruits, nuts, beans, dairy products, and grains.[19]

5-methyltetrahydrofolate:

- 5-MTHF is the metabolically active form of folate and is the transported form of folate in the plasma.[20] It provides useable folate to the body that circumvents the need for activation of the MTHFR enzyme. It also avoids interaction with drugs that have an effect on dihydrofolate reductase (DHFR) such as methotrexate. Dosing begins at 400 mcg daily and increases up to 15 mg daily depending on health conditions and patient tolerance.[21]

L-5-formyltetrahydrofolate:

- L-5-formyltetrahydrofolate (folinic acid) is the reduced form of folic acid. It does not require dihydrofolate reductase (DHFR) conversion and is a preferred form of folate in patients undergoing methotrexate or other DHFR inhibiting therapies. Supplement levels up to 5 mg daily have been utilized to reduce homocysteine levels.[22,23]

SUPPLEMENTAL INTERVENTIONS

Additional B Vitamins

B12 (cobalamin):

- B12 is a necessary cofactor in the production of methionine from homocysteine. The methionine synthase enzyme utilizes B12 and 5-MTHF to regenerate methionine. The preferred form of B12 is methylcobalamin as the required methyl group is present for the re-methylation process.[24] Recommended dose begins at 500 mcg daily.[22]

B6 (pyridoxine):

- B6 is required for the cystathionine β-synthase (CBS) enzyme to process homocysteine into cystathione and eventually cysteine in the transulfuration pathway. CBS uses the active B6 pyridoxal-5'phosphate (PLP) as the cofactor.[25] Supplementation with PLP ensures that adequate homocysteine regulation occurs. Recommended dosing begins at 25 mg daily.[22]

B2 (riboflavin):

- Riboflavin makes up a part of the flavin-adenine-dinucleotide (FAD) cofactor involved in the MTHFR pathway. Supplementation of at least 2.1 mg daily in variant allele carriers shows improvement in enzyme function.[26]

Betaine/Trimethylglycine

Hyperhomocysteinemia and hyperhomocysteinuria are common consequences of MTHFR polymorphisms. In patients with elevated homocysteine levels, supplementation with betaine anhydrous/ trimethylglycine (TMG) helps to effectively reduce these levels to a more therapeutic range. Recommended dose is 250 mg daily up to 3 gms daily in cases of homocysteinuria.[26,27] If treating with high dose betaine it is recommended to check for CBS polymorphisms as this may lead to elevated levels of methionine that may result in cerebral edema.[27,28]

NAC: N-acetylcysteine

NAC benefits hyperhomocysteinemia patients by mobilizing homocysteine from its binding proteins, namely albumin, in the plasma. This allows the homocysteine to be properly metabolized while also exerting a protective effect over the production of reactive oxygen species (ROS).[29]

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KASHI CLINICAL LABORATORIES

COMT

Genetic Analysis Report

PATIENT
PFirst PLast
DOB: 01/01/72

ORDERING PROVIDER
Example Organization

LABORATORY INFORMATION

Lab ID:	N8C9841
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COMT GG

The patient's genotype for COMT suggests rapid breakdown of catecholamines, most notably dopamine. A patient with this genotype may require higher doses of pain medication. A diet high in tyrosine may support continuous neurotransmitter production. Some research has found that the polyphenols EGCG and quercetin may inhibit the COMT enzyme.

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ASSAY	RESULT	PHENOTYPE	ENZYME ACTIVITY
COMT	G/G	Normal	High

CLINICAL CONSEQUENCES

Homozygous Val/Val allele carriers exhibit higher COMT enzyme activity and thus have an increased capacity to degrade catecholamines; this can contribute to lower dopamine levels and a higher pain tolerance. Despite being more resilient to pain, Val/Val genotypes often require higher doses of morphine to obtain the same pain relief as other genotypes. Val/Val allele carriers may have an enhanced response to COMT inhibitors used in Parkinson's disease treatment and may have lower estradiol levels than those expressing other alleles.

COMT BACKGROUND INFORMATION

The COMT (catechol-O-methyltransferase) gene codes for the essential COMT enzyme that is involved in the inactivation of catecholamines such as dopamine, epinephrine, norepinephrine and catecholestrogens.[1-3] Scientific research has demonstrated that a common mutation in the COMT locus results in the replacement of the amino acid valine with methionine at position 158 in the enzyme. This causes a dramatic reduction in the enzyme's ability to metabolize these neurotransmitters and catecholestrogens.[1,4] The enzyme is notably active in the prefrontal cortex (PFC), the area of the brain that gives rise to what we perceive as personality, emotions, behavior inhibition, abstract thinking, and short-term memory.[5] Val/Val allele carriers have higher enzyme activity resulting in greater stress resiliency and lower dopamine levels, while Met/Met allele carriers have lower enzyme activity resulting in reduced stress resiliency and higher dopamine levels. Heterozygous Val/Met allele carriers exhibit an intermediate enzyme activity. Polymorphisms in the COMT gene have been implicated in association with various mental health disorders through the resulting changes in dopamine levels.[1,2,5,6] Depending on the variant, associated disorders include drug abuse,[7] alcohol abuse,[8] severity of schizophrenic symptoms,[9,10] obsessive compulsive disorder in men,[11] panic disorder,[12] post-traumatic stress disorder,[13] and bipolar affective disorder.[14,15] Having a particular polymorphism does not mean that someone will develop one or more of the associated disorders.

Summary of Likely Patterns Associated with COMT Alleles

GENE ALLELE	ENZYME ACTIVITY	DOPAMINE LEVELS	PAIN RESPONSE	PAIN MED NEED	STRESS RESILIENCY	ESTRADIOL LEVELS
Val/Val	HIGH	LOWER	MORE TOLERANCE	POSSIBLE HIGHER DOSE	HIGHER	LIKELY LOWER
Val/Met	BALANCED	AVERAGE	AVERAGE	AVERAGE	AVERAGE	AVERAGE
Met/Met	LOW	HIGHER	MORE ACUTE	PROBABLY LOWER DOSE	REDUCED	LIKELY HIGHER

PAIN MANAGEMENT AND NEUROLOGICAL INFORMATION

COMT polymorphisms have been linked to pain sensitivity.[16,17] It has been suggested that a reduction in dopamine inactivation, such as is seen with the Met/Met genotype, results in higher levels of dopamine, leading to chronic stimulation of the dopamine receptors. This overstimulation may result in less endogenous opioids being produced that help to provide pain relief and euphoria.[17] Therefore, Met/Met allele carriers can perceive a higher level of pain, while Val/Val carriers have the greatest resistance to pain.[16,17] Interestingly, studies have shown that Met/Met allele carriers require less morphine to achieve pain relief, possibly due to the increase in μ-opioid receptors seen with this genotype, while Val/Val allele carriers require the most medication for pain management.[18] COMT also has been shown to have an effect on L-DOPA therapy in Parkinson's disease treatment.[19] Commonly COMT inhibitors, such as entacapone, are utilized in Parkinson's treatment to augment and prolong L-DOPA treatment.[20] COMT polymorphisms affect the bioavailability of these medications, yielding a heightened effect of entacapone in the Val/Val allele carriers as compared to Met/Met allele carriers.

ESTRADIOL INFORMATION

COMT has also been demonstrated to play a role in estrogen metabolism through inactivation of the catecholestrogens.[21] Catecholestrogens are formed during the metabolism of estrogens such as estradiol. Catecholestrogen inactivation decreases the cancer-causing potential of these metabolites, while simultaneously increasing the amount of 2-methoxyestradiol, a metabolite that has been shown to inhibit the growth of breast cancer cells.[4,22,23] Additionally, COMT polymorphisms have been shown to exert an effect on estradiol levels.[24] As Met/Met allele carriers exhibit a 2-3 fold decrease in their ability to degrade catecholestrogens, this results in higher estradiol levels than Val/Val allele carriers.[4,25] Estradiol clearance is also diminished in both the Met/Met and Met/Val genotypes as opposed to Val/Val genotypes, however there is no significant difference in estrone levels.[24]

TREATMENT CONSIDERATIONS

Homozygous Valine (Val/Val) allele carriers have lower dopamine levels. Increasing certain amino acids without proper balance of all neurotransmitters may result in increased cognitive symptoms.[32]

- L-Tyrosine is an amino acid and a precursor to dopamine. [33] Dopamine precursors may be supportive of dopamine production; however, L-tyrosine's use in the treatment of individuals with the Val/Val genotype is theoretical as there have been no studies performed validating its effectiveness.
- COMT polymorphisms, specifically Val/Val homozygotes, may influence the plasma levels of homocysteine. [44] Individuals with high levels of homocysteine may benefit from supplementation with melatonin, which may lower homocysteine. [45]
- Active B Complex vitamins are associated with the proper methylation of enzymes throughout the body and may lower homocysteine, while high levels of homocysteine are associated with cognitive impairment.[28-31]
- Green tea may suppress COMT function, increase dopamine release, and suppress the production of reactive oxygen species, thereby inhibiting inflammatory responses. [46-49] Additionally, intake of caffeine may support dopamine neurotransmission in conditions with dopamine deficiency.[50]
- A small study in elderly adults found that increasing unsaturated fatty acids along with caloric restriction modulates cognition in homozygous (Val/Val) allele carriers.[51]
- A small study in elderly adults found that physical activity improves cognition in homozygous (Val/Val) allele carriers.[52]

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