Kashi Clinical Laboratories, Inc.
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KASHI HEALTH

Delivering More Than a Test Result

ASHI No. 10-4-OR-03-1
CLIA No. 38D1058476

MTHFR GENOTYPING REPORT

Patient Name:	Johnny Health	Date Sample Collected:	00/00/14
DOB:	00/00/14	Date Sample Received/Tested:	00/00/14
Lab ID Number:	000000000	Date Reported:	00/00/14
Ordering Physician:	Dr. KCL	Ordering Facility:	Acme Center

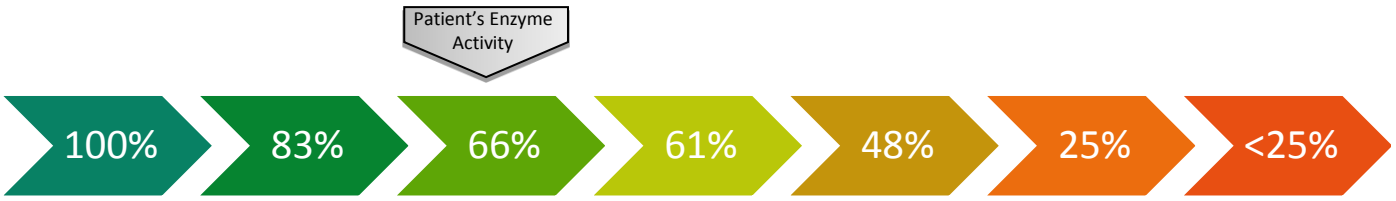
PATIENT'S TEST RESULTS AND INDICATIONS

TEST	GENOTYPE	RESULT
C677T Mutation	C/T	Positive
A1298C Mutation	A/A	Negative

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

- Heterozygosity for C677T is associated with intermediate levels of enzyme activity.
- Not at risk for increased homocysteine levels.
- Shows an intermediate risk level for depression.
- Increased sensitivity to Methotrexate leading to lower dosage requirements, increased side effects or intolerance of the drug.
- The patient's genotypes should be interpreted in light of clinical information.

PATIENT'S APPROXIMATE MTHFR ENZYME ACTIVITY[1]



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.

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MTHFR BACKGROUND INFORMATION (continued)

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 C677T or A1298C variant alleles and the compound heterozygous state (presence of both heterozygous genotypes C677T/ A1298C). 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 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]

MTHFR: CARDIAC HEALTH INFORMATION

An elevated homocysteine level has been identified as an independent risk factor for ischemic stroke, thrombotic and cardiovascular diseases.[5,6,14] 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.

This test was developed and its performance characteristics determined by Kashi Clinical Laboratories. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Reported and Reviewed By:

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

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MTHFR TREATMENT OPTIONS

NOTICE: These recommendations do 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.

Based on the patient's genotype, the following supplements are recommended as requirements to fully support the patient's folate metabolism pathway.

	MTHFR Genotype	Supplement	Starting Dosage Range	Notes
✓	C/T A/A	L-5-MTHF or L-5-FTHF	400mcg – 15 mg	Using an active form of folate is crucial as the patient's ability to generate active folate is compromised.
✓	C/T A/A	Methylcobalamin (B12)	500mcg (sublingual preferred)	Using the active form of Vitamin B12 ensures the patient has the necessary methyl groups to regenerate the active folate.
✓	C/T A/A	Active B Complex	Should include as a minimum: 25mg Pyridoxal-5-phosphate (B6) 2.1mg riboflavin-5'-phosphate (B2)	An active B complex will help to supply the patient with the other necessary cofactors to support 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

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.[1]
- Avoid smoking: smoking has been shown to elevate homocysteine levels.[1]

Folate:

Folate rich diet:

Eating a folate rich diet provides greater amounts of substrate for the enzyme. Aiming for 400mcg daily from various sources is recommended for most individuals, 600-800 mcg daily should be consumed by pregnant women.[2,3] Sources include: liver, dark leafy green vegetables, fruits, nuts, beans, dairy products, and grains, as well as fortified foods.[3]

5-methyltetrahydrofolate:

5-MTHF is the metabolically active form of folate and is the transported form of folate in the plasma.[4] 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 400mcg daily and increases up to 15 mg daily depending on health conditions and patient tolerance.[5]

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.[6,7]

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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.[8] Recommended dose begins at 500 mcg daily.[6]

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.[9] Supplementation with PLP ensures that adequate homocysteine regulation occurs. Recommended dosing begins at 25 mg daily.[6]

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 mutation carriers shows improvement in enzyme function.[10]

Betaine/Trimethylglycine:

Hyperhomocysteinemia and hyperhomocysteinuria are common sequelae 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 250mg daily up to 3 gms daily in cases of homocysteinuria.[10,11] 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.[11,12]

NAC: N-acetylcysteine

NAC benefits hyperhomocysteine 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).[13]

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