COMT GENOTYPING REPORT

Patient Name: Johnny Health
DOB: 00/00/14
Lab ID Number: 000000000
Ordering Physician: Dr. KCL

Date Sample Collected: 00/00/14
Date Sample Received/Tested: 00/00/14
Date Reported: 00/00/14
Ordering Facility: Acme Center

PATIENT'S TEST RESULTS AND INDICATIONS

<table>
<thead>
<tr>
<th>TEST</th>
<th>GENOTYPE</th>
<th>RESULT</th>
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<tbody>
<tr>
<td>Val158Met Mutation</td>
<td>A/A</td>
<td>Met/Met</td>
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</table>

This patient carries a Val158Met gene mutation resulting in Homozygous Met/Met alleles.

- Indicates a 3-4 fold reduction in enzyme activity.
- Reduction in stress resiliency.
- Higher dopamine level.
- Carriers tend to perceive a higher level of pain, yet may have a decreased requirement for morphine in pain relief.
- May have a diminished response to COMT inhibitors in Parkinson’s disease treatment as compared to Val/Val allele carriers.
- Indicates reduced capacity to degrade catecholamines and may have higher estradiol levels as compared to Val/Val genotypes.

PATIENT'S APPROXIMATE COMT ENZYME ACTIVITY²

- High Activity
- Balanced Activity
- Low Activity

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 and norepinephrine and catecholestrogens.¹ ² ³ ⁴ Scientific research has demonstrated that a common mutation in the COMT locus results in the conversion of the amino acid valine to methionine at position 158, and causes a dramatic reduction in the enzyme’s ability to metabolize these neurotransmitters and catecholestrogens.¹ ² ⁴ The enzyme is notably active in the prefrontal cortex, or PFC; the area of the brain that gives rise to what we perceive as our personality, emotions, behavior inhibition, abstract thinking, and short-term memory.⁵ Val allele carriers have higher enzyme activity resulting in greater stress resiliency and lower dopamine levels, while Met allele carriers have lower enzyme activity resulting in reduced stress resiliency and higher dopamine levels, and heterozygous Val/Met allele carriers exhibit an intermediate enzyme activity.
MENTAL HEALTH INFORMATION

Polymorphisms in the COMT gene have been implicated in association with various mental health disorders through the resulting changes in dopamine levels.\(^1\,\,^2\,\,^3\,\,^4\) Disorders that may be associated with this gene variant in some populations 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.\(^14\,\,^15\)

PAIN MANAGEMENT INFORMATION AND NEUROLOGICAL INFORMATION

COMT polymorphisms have also 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 perceive a higher level of pain, while Val/Val carriers have the greatest resistance to pain.\(^16\,\,^17\) Interestingly though, studies have shown that Met/Met allele carriers require less morphine to achieve pain relief, possibly due to the increase in \(\mu\)-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 an enhanced 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.\(^21\) This inactivation step lowers 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.\(^5\,\,^22\,\,^23\) 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.\(^6\,\,^25\) 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.\(^24\)

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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COMT 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.

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Starting Dosage Range</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>✓ S-adenosyl methionine (SAMe)</td>
<td>4,000-1,600 mg/day</td>
<td>SAMe is an important methyl group donor involved in many of the biochemical and enzyme structures in the body. Specifically, it is involved in the synthesis of the COMT enzyme and involved in folate metabolism. Additionally, SAMe may be useful in the treatment of depression. 26-29</td>
</tr>
<tr>
<td>✓ Magnesium</td>
<td>200-600 mg/day, or to bowel tolerance.</td>
<td>Magnesium is required for the proper synthesis of the COMT enzyme in addition to proper function many other enzyme complexes throughout the body. Deficiency is associated with depression and poor cognition. 30-33</td>
</tr>
<tr>
<td>✓ Active B Complex</td>
<td>Daily RDA or 50 mg BID</td>
<td>Active B Complex vitamins are associated with proper methylation of enzymes throughout the body and may lower homocysteine, where high levels are associated with cognitive impairment. 34-37</td>
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OPTIONAL DEPENDING ON HEALTH CONDITIONS AND PROVIDER DISCRETION
Homzygous methionine (Met/Met) allele carriers have higher dopamine levels as well as other neurotransmitters or catecholamines. If dopamine precursors (L-tyrosine, L-dopa) are not in balance with serotonin (L-tryptophan, 5-HTP) precursors, depletion of neurotransmitters may occur. 38-41

- **L-Tryptophan** is an essential amino acid and precursor to melatonin and serotonin and building block for proteins. This may be effective for patients with a deficiency in serotonin levels and depression. 42-43
- **L-5-Hydroxytryptophan (5-HTP)** is a metabolite of L-tryptophan and the precursor to serotonin. 5-HTP bypasses the rate-limiting enzyme in serotonin synthesis. Supplementation of 5-HTP may be useful as adjunctive treatment for depression. 44-45
- **L-Theanine** is a constituent and amino acid found in green tea that has demonstrated improvement in cognitive function in neurological conditions. 46-50

RECOMMENDED LIFESTYLE INTERVENTIONS

- **Avoid Phenylalanine, L-Tyrosine and L-Dopa supplements, and excessive vitamin C.** Phenylalanine and L-tyrosine are essential and aromatic amino acids, and are both precursors to dopamine. L-tyrosine is a precursor to catecholamines, and is synthesized from phenylalanine. L-Dopa is also a precursor to catecholamine synthesis, which requires ascorbate to synthesize norepinephrine from dopamine. 51-52

- **Avoid foods that contain tyramine, such as cheese and wine, as it is converted into dopamine endogenously as well as triggering dopamine release and catecholamines.** Tyramine is a trace amine synthesized from enzymatic conversion of tyrosine. 53-55

- **Homzygous (Met/Met) allele carriers may respond to anti-depressants slower than other polymorphisms.** Aerobic exercise three times per week adjunctive to pharmacotherapy may improve depression. 56-57
RECOMMENDED LIFESTYLE INTERVENTIONS (Continued)

- **COMT expression is inhibited by estrogens**, thus COMT activity is lower in females than males, and the sex/and hormonal status of each individual should be considered while balancing hormones. Additionally, **estrogen enhances dopamine effects**, further emphasizing the importance of appropriately balancing hormones.\(^{58-59}\) **Estrogen Metabolism is diminished in homozygous (Met/Met) carriers**, and as a result it may be useful to improve metabolism through dietary intervention with ground flax seed daily.\(^{60-61}\)

- Within tissues outside the liver estrogens are metabolized by phase I and phase II metabolic enzymes. **Selenium rich foods, such as cruciferous vegetables**, can increase metabolism resulting in increased clearance of estrogen metabolites.\(^{62-64}\)

- **Daily intake of green tea and other polyphenols and flavonoids** may assist in the metabolism of estrogen, and improve neurocognitive conditions.\(^{65-67}\)

Background References:
Treatment References:
Treatment References:


