



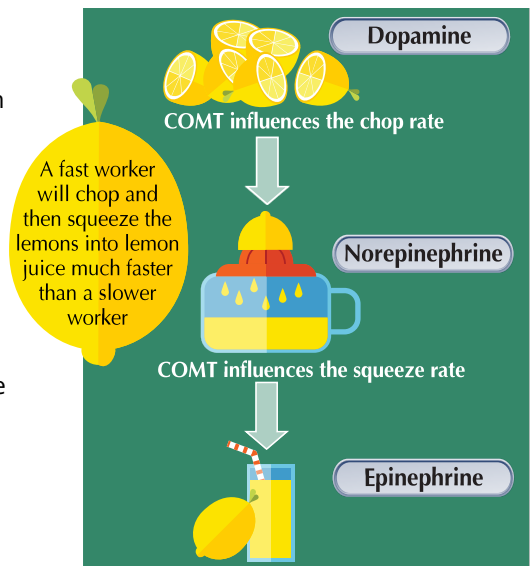
PATIENT: Vpcaj Rxjgf DOB: 09/27/46	ORDERING PROVIDER: Dr. Ronald Hunninghake Jtx-Ljpydn Hmp	LABORATORY INFORMATION: Lab ID Number: 170126039HLA Sample Collection Date: 01/24/17 Sample Test Date: 01/26/17 Report Date: 02/02/17
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GENE MARKER	BALANCED	TEST RESULT	ENZYME ACTIVITY	COMMENT
Val158Met	G/A Val/Met	A/A Met/Met	● Reduced	Homozygous Met/Met allele carriers typically have an approximately 3-4 fold reduction in enzyme activity and thus a reduced capacity to degrade catecholamines. This can contribute to higher dopamine levels, a reduced stress resiliency, and enhanced pain perception, yet there may be a decreased requirement for morphine in pain relief. Met/Met allele carriers may have a diminished response to COMT inhibitors in Parkinson's disease treatment and may have correspondingly higher estradiol levels than other genotypes.

RISK ALLELE KEY: ○ No Risk ● Risk Allele Heterozygous ● Risk Allele Homozygous

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



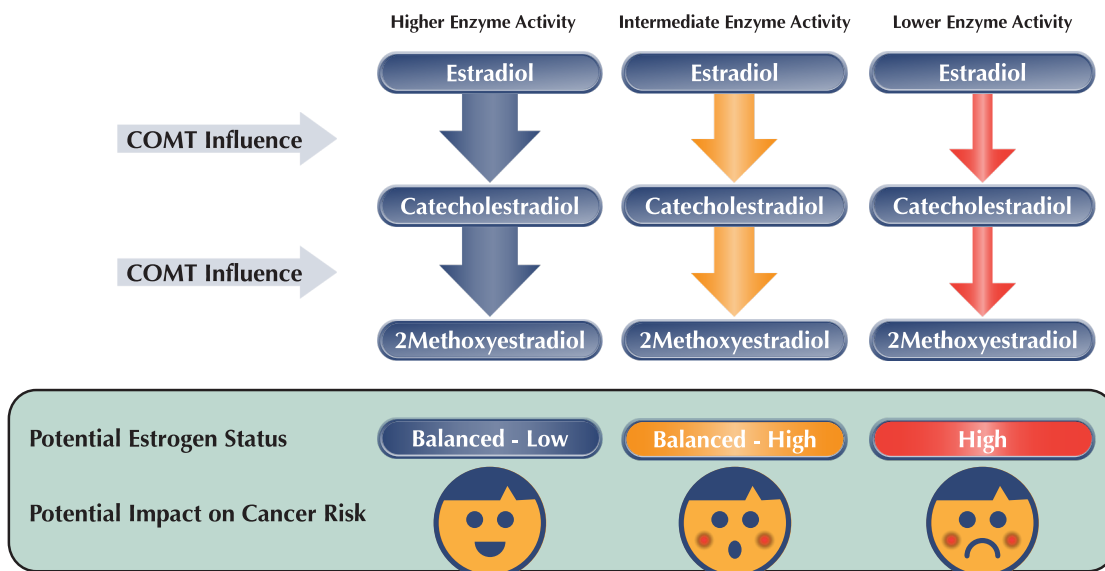
PAIN MANAGEMENT AND NEUROLOGICAL INFORMATION

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. Catecholesterogen 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

ENZYMATIC PROCESS OF COMT (RELATED TO ESTROGEN STATUS AND CANCER RISKS)





TREATMENT CONSIDERATIONS

Homozygous Methionine (Met/Met) allele carriers have higher dopamine levels. Increasing certain amino acids without proper balance of all neurotransmitters may result in increased cognitive symptoms.³²

- 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 in folate metabolism. Additionally, SAME may be useful in the treatment of depression.^{26,27}
- Magnesium is required for the proper synthesis of the COMT enzyme, and for the proper function of many other enzyme complexes throughout the body.⁵⁷ Deficiency is associated with depression and poor cognition.⁵⁸⁻⁶⁰
- Active B Complex vitamins are associated with proper methylation of enzymes throughout the body and may lower homocysteine, where high

levels of homocysteine are associated with cognitive impairment.²⁸⁻³¹

- Avoid foods that contain tyramine, such as cheese and wine, as it is converted into dopamine endogenously and may trigger dopamine and catecholamine release. Tyramine is a trace amine synthesized from enzymatic conversion of tyrosine.^{32,33}
- Estrogen Metabolism is diminished in homozygous Met/Met allele carriers, and as a result it may be useful to improve metabolism through dietary intervention with ground flax seed daily.⁵³
- COMT expression is inhibited by estrogens, thus COMT activity is lower in females than males, and the sex/hormonal status of each individual should be considered while balancing hormones. Additionally, estrogen enhances dopamine effects, further emphasizing the importance of appropriately balancing hormones.⁵⁴⁻⁵⁶

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.

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