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. 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. 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. 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. COMT polymorphisms have also been linked to pain sensitivity. It has been suggested that a reduction in dopamine inactivation, such as 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. Therefore, Met/Met allele carriers perceive a higher level of pain, while Val/Val carriers have the greatest resistance to pain. Interestingly though, 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.

COMT also has been shown to have an effect on L-DOPA therapy in Parkinson’s disease treatment. Commonly COMT inhibitors, such as entacapone, are utilized in Parkinson’s treatment to augment and prolong L-DOPA treatment. 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.

COMT has also been demonstrated to play a role in estrogen metabolism through inactivation of the catecholestrogens. 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. Additionally, COMT polymorphisms have been shown to exert an effect on estradiol levels. 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. 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.
References:

Test systems were validated and their performance characteristics determined by the Kashi Clinical Laboratories and under the accreditation guidelines of the Clinical Laboratory Improvement Amendments (CLIA). Some tests have not been cleared or approved by the U.S. Food and Drug Administration.

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