MTHFR Polymorphism

MTHFR polymorphism refers to variations in the MTHFR (methylenetetrahydrofolate reductase) gene. This gene provides instructions for producing the MTHFR enzyme, which is involved in the metabolism of folate (vitamin B9) in the body. Folate is essential for various biochemical processes, including DNA synthesis, repair, and methylation—a chemical process that regulates gene expression.

One of the most well-known variations in the MTHFR gene is the C677T polymorphism, where cytosine (C) is replaced by thymine (T) at position 677. This genetic variation can lead to reduced enzymatic activity of MTHFR, which in turn affects the body's ability to metabolize folate properly. This can result in elevated levels of homocysteine, an amino acid that, when present at high levels, is associated with an increased risk of cardiovascular disease, stroke, and other health issues.

Another common MTHFR polymorphism is A1298C, where adenine (A) is replaced by cytosine (C) at position 1298. This variant can also impact MTHFR enzyme activity and contribute to elevated homocysteine levels.

MTHFR polymorphisms have been studied for their potential associations with various health conditions, including cardiovascular disease, neural tube defects, pregnancy complications, and mental health disorders. However, the relationship between MTHFR polymorphisms and these conditions is complex and not fully understood. While some studies suggest a possible link, the overall impact of MTHFR polymorphisms on health is influenced by various genetic and environmental factors.

It's important to note that MTHFR polymorphisms are common and can be present in a significant portion of the population. However, not everyone with these polymorphisms will experience negative health effects. If you are concerned about MTHFR polymorphisms and their potential impact on your health, it's a good idea to consult a medical professional or a genetic counselor. They can provide personalized information and guidance based on your specific situation and health history.

The folate-antagonist methotrexate (HD-MTX) is integral to induction chemotherapy for Primary central nervous system lymphoma; however, it can be associated with leukoencephalopathy. Methylenetetrahydrofolate-reductase (MTHFR) is involved in intracellular folate depletion.

Karschnia et al. assessed whether MTHFR polymorphisms affect the risk for leukoencephalopathy.

They retrospectively searched the database at the Massachusetts General Hospital for newly diagnosed PCNSL treated with HD-MTX (without radiotherapy nor intrathecal chemotherapy).

Among 68 PCNSL patients, MTHFR polymorphisms were found in 60 individuals (88.2%) including a 677C→T genotype, a 1298A→C genotype, or a combined 677C→T/1298A→C genotype. Neither MTX clearance nor response to induction therapy was affected by specific genotypes, and complete response was achieved in 72.1% of patients by HD-MTX-based induction. However, the 1298A→C genotype was associated with increased frequency and severity of leukoencephalopathy over time (odds ratio: 4.0, CI 1.5-11.4). Such genotype predicted treatment-induced leukoencephalopathy with a sensitivity of 71.0% and a specificity of 62.2% (AUC: 0.67, CI 0.5-0.8; p=0.019). While progression-free survival did not differ in genotype-based subgroups, overall survival was lower for the 1298A→C genotype.

The MTHFR 1298A→C genotype may serve to identify PCNSL patients at elevated risk for HD-MTX-induced leukoencephalopathy. This appears to translate into reduced survival, potentially due to decreased functional status [1)].

1)

Karschnia P, Kurz SC, Brastianos PK, Winter SF, Gordon A, Jones S, Pisapia M, Nayyar N, Tonn JC, Batchelor TT, Plotkin SR, Dietrich J. Association of MTHFR Polymorphisms With Leukoencephalopathy Risk in Primary CNS Lymphoma Patients Treated With Methotrexate-Based Regimens. Neurology. 2023 Aug 1:10.1212/WNL.0000000000207670. doi: 10.1212/WNL.0000000000207670. Epub ahead of print. PMID: 37527941.

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