THE ROLE OF MUTATION IN THE MTHFR GENE OF POLYMORPHISM 677 C/T IN PATIENTS WITH CARDIOVASCULAR INSUFFICIENCY

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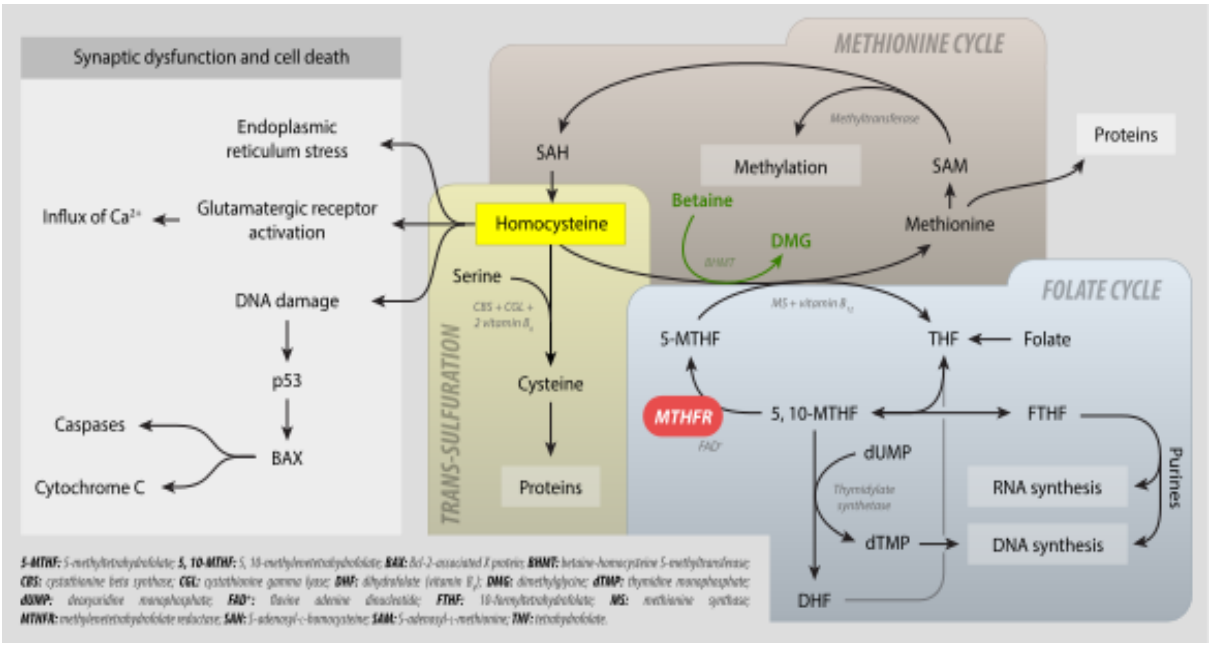
Abstract: The MTHFR gene is located on the 1st human chromosome, p 36.3, it is responsible for the synthesis of the enzyme Methylenetetrahydrofolate Reductase (MTHFR) to date, more than 20 + polymorphisms of this gene are known to exist. The main function of this enzyme is to participate in the conversion of homocysteine to methionine in the presence of cofactors – pyridoxine (vitamin B6) and cyanocobalamin (vitamin B12) – and a substrate – folic acid. In this literature review, we are interested in polymorphism 677 C/T, where Cytosine being replaced by Thymine leads to the replacement of valine in amino acid 222, as a result, a thermolabile enzyme with reduced activity is encoded. In Figure 1, you can see the work of the MTHFR enzyme.



In addition, 5-METHYLTHF, a product of MTHFR, provides a methyl group for remethylation of homocysteine to methionine, thereby providing the production of S-adenosyl methionine (SAM), necessary for most biological methylation reactions, including the cytosine reaction located in cytosine guanine (CpG) dinucleotide DNA sequences. With a high content of folic acid and related nutrients in the diet, people with this polymorphism may have a lower risk of developing cancer, since higher intracellular levels of 5.10-methylentgf can prevent nucleotide imbalance, during DNA synthesis, thereby ensuring DNA replication with high. In addition, with a high intake

of folic acid and related cofactors, the flow of 5.10-methylenthf to 5-METHYLTHF will function at full capacity, and, consequently, people with this polymorphism will have adequate SAM levels for optimal DNA methylation. When the intake of folic acid and related nutrients is low, a decrease in the stability of the MTHFR variant leads to deactivation of the MTFHR enzyme and, consequently, a decrease in the flow of 5.10-methylentgf towards the methionine cycle at a higher threshold of folic acid availability. This will support the availability of 5.10-methylentgf and reduce the likelihood of violations of DNA synthesis and subsequent nucleotide imbalance. However, in this case, DNA methylation may be disrupted due to a decrease in the level of 5-METHYLTHF as a result of insufficient intake from food and a decrease in the flow of 5.10-methylenthf into the methionine cycle due to a decrease in the stability of the MTHFR enzyme variant. DNA damage, genome instability and disruption of DNA repair as a result of nucleotide imbalance are important mechanisms of carcinogenesis. Both hypomethylation of genomic DNA and hypermethylation of a gene-specific CpG promoter islet are also important epigenetic mechanisms of carcinogenesis. However, these putative functional effects of the C677T MTHFR polymorphism have not yet been clearly demonstrated in target organs. There is reliable evidence that Carriers of the CC genotype have the most common genotype. TT individuals (homozygous for 2 alleles) have lower MTHFR activity than CC or CT individuals (heterozygous). About 10% of the population of North America are carriers of the TT genotype. There is an ethnic variability in the frequency of the T allele - the frequency among Mediterranean/Latin Americans is higher than that of Caucasians, who, in turn, are higher than that of Africans/African Americans.The degree of thermal stability of enzymes (estimated as residual activity after thermal inactivation) is significantly higher in people with the TT genotype (18-22%) compared with CT (56%) and CC (66-67%) genotypes. Are people with the TT genotype predisposed to mild, hyperhomocysteinemia (high levels of homocysteine in the blood), because they have less active MTHFR, capable of producing 5-methyltetrahydrofolate (which is used to reduce homocysteine levels). Low intake of vitamin folic acid with food can also cause mild hyperhomocysteinemia. Low folic acid intake affects people with TT genotype to a greater extent than people with CC/CT genotype inclusive. People with TT genotype (but not CC/CT) with lower folic acid levels in plasma, they are at risk of elevated levels of homocysteine in plasma. In human recombinant MTHFR studies, the protein encoded by 677T loses its FAD cofactor three times faster than wild-type protein 5-methyl-THF slows down the rate of FAD release in both wild-type and mutant enzymes, although to a much greater extent in mutant enzymes. The low status of folic acid with the subsequent loss of FAD increases the thermal stability of the enzyme, which explains the normalized levels of homocysteine and DNA methylation in people with a high content of folic acid, and with the TT genotype. This

polymorphism and hyperhomocysteinemia are associated with neural tube defects in offspring, an increased risk of pregnancy complications and other pregnancy complications, arterial and venous thrombosis and cardiovascular diseases. 677TT people have a reduced risk of developing acute lymphoblastic leukemia and colon cancer. Mutations in the MTHFR gene may be one of the factors leading to an increased risk of developing schizophrenia. Patients with schizophrenia who have a risk allele (TT) show more deficiencies in executive function tasks. There is also a weakly positive association between MTHFR mutations and dementia. One study of elderly Japanese found a correlation between carriers of the CT genotype, Apo E polymorphism and certain types of senile dementia. Another study found that people with folic acid-related mutations may still have functional deficits even when blood folic acid levels are within normal limits, and methyltetrahydrofolate supplementation was recommended for potential prevention and treatment of dementia (along with depression). A 2011 study in China also found that SNP C677T was associated with Alzheimer's disease, in Asian populations (but not in Caucasians). Polymorphism C677T is associated with the risk of myocardial infarction in residents of Africa, North America and the elderly. In addition, hypermethylation of the aberrant MTHFR promoter is associated with male infertility. Moreover, this inadequate epigenetic phenomenon was observed in sperm samples of infertile men belonging to couples with a history of recurrent spontaneous abortion. Improper hypermethylation of the MTHFR promoter can affect two main roles of DNA methylation in spermatogenic cells, the process of global genome methylation and genomic imprinting of paternal genes. In addition, hypermethylation of the MTHFR gene promoter was also associated with loss of methylation of the imprinted H19 gene in sperm samples of infertile men. Hyperhomocysteinemia (HCA) is known to be associated with an increased tendency to thrombosis, is considered as a risk factor for coronary heart disease and atherosclerosis, while others do not find a link between acute myocardial infarction (MI) and HCA. Mild to moderate HCA is known to occur due to genetic factors, such as a mutation in the methylenetetrahydrofolate reductase (MTHFR) genes, or due to environmental factors, such as vitamin B12 deficiency or folic acid. It is known that the presence of the C677T mutation correlates with increased thermal stability of MTHFR, and homozygotes for the C677T allele are predisposed to HCA in the context of the suboptimal status of folic acid. Vitamin interventions are known to reduce the level of homocysteine (Hcy), an endothelial toxin that is involved in the pathogenesis of coronary heart disease.

Research citations from 2012 (Indian J Med Res. 2012 Apr; 135(4): 506-512). The research team conducted an analysis, followed by statistical processing with the aim of identifying statistical reliability. The study included 199 consecutive angiographically confirmed patients with coronary heart disease under the age of 45

years without any other known procoagulant condition and 200 healthy control group individuals of the same age and gender. Fasting blood samples were collected in EDTA, plasma Hcy was evaluated using the ELISA test, and the determination of MTHFR C677T polymorphism was performed by real-time PCR (genotyping). A significant difference (P <0.001) was found between the average levels of Hcy in fasting plasma in cases (22.14 ± 10.62 mmol/L) and controls (17.38 ± 8.46 mmol/L) with odds ratio as 1.93 (95% CI, 1.27-2.94). The levels of cholesterol, LDL and triglycerides were significantly (P <0.001) higher in the cases compared to the control group. The study showed a significant correlation between hyperhomocysteinemia and coronary heart disease. Multivariate analysis using logistic regression of various CHD risk factors revealed high levels of hemoglobin, cholesterol, LDL and low HDL levels and smoking as independent predictors of CHD when all other factors were controlled. The significant reduction after treatment found in HCA was easily modifiable by vitamin intervention regardless of their genotype.

Genotype	Cases		Cotrols		Stat test and *P* value
	N (%)	Hcy levels in μ mol/l	N (%)	Hcy levels in μ mol/l	
CC	132 (66.3)	21.67 ± 10.84	154 (77.5)	17.38 ± 8.01	t=3.839 *P*=0.001
CT	64 (32.2)	23.58 ± 9.00	45 (22.0)	16.83 ± 9.41	t=3.783 *P*=0.001
TT	3 (1.5)	45.53 ± 14.71	1 (0.5)	30.4 (single value)	NA
Total	199 (100)	22.14 ± 10.62	200 (100.0)	17.38 ± 8.46	t=5.445 *P*=0.000

*P<0.001 compared with controls, values are mean ± SD

Conclusion: It is interesting that carriers of the TT genotype in both groups had a high content of Hcy in blood plasma. Carriers of the TT genotype had a high concentration of Hcy in blood plasma by 2.10 times (p>0.001), and a high concentration of Hcy in blood plasma was also found in a conditionally healthy person with the same genotype (TT) by 1.749 (p>0.001) times than the carrier of the CT and CC genotype inclusive. Interestingly, carriers of the TT genotype in both groups had a high content of Hcy in blood plasma. Hyperhomocysteinemia is a multifactorial disease, and in this regard, the presence of the genotype (TT) in patients with cardiovascular insufficiency cannot indicate a severe course of the disease, or remission. But for the sake of fairness, it should be noted that in those people who led an unhealthy lifestyle, ate food containing HDL, while abusing smoking, genotyping

of this category of people is a reliable way of early diagnosis of coronary heart disease, thereby contributing to the prevention of the disease.

Used literature:

1.Indian J Med Res. 2012 April; 135(4): 506-512

2. Alfthan G, Pekkanan J, Jauhiainen M, Pitkäniemi J, Karvonem M, Tuomilehto J. Association of serum concentrations of homocysteine and lipoprotein (a) with atherosclerotic disease in a prospective Finnish population study. Atherosclerosis. 1994; 106 : 9-19.

3. Farachi FM. Hyperhomocysteinemia: a million ways to lose control. Arteriosclerosis Thrombus Basic Biol. 2003; 23 :371-3.

4. Wald D.S., Low M., Marris J.K. Homocysteine and cardiovascular diseases: evidence of a causal relationship from meta-analysis. BMJ. 2002; 325 :1202-1206.

5. Schnyder G, Roffi M, Pin R, Flammer Y, Lange H, Eberli FR, et al. Reduction of the frequency of recurrent coronary artery stenosis after a decrease in plasma homocysteine levels. N Engl J Med. 2001; 345: 1593-600.

6. Lewis S.J., Shah E., Smith G.D. Meta-analysis of MTHFR 677 C→T polymorphism and coronary heart disease. Does the body of evidence support the accidental role of homocysteine and the preventive potential of folic acid. BMJ. 2005; 331: 1053-70.

7. Clark R., Bennett D.A., Parish S., Verhuf P., Detsh-Clerk M. et al. Homocysteine and coronary heart disease: A meta-analysis of MTHFR case-control studies, avoiding publication bias. PLOS Med. 2012; 9 (2): e1001177.

8. Fletcher O., Kessling A.M. Connection of MTHFR with atherosclerotic vascular disease? Ham Wife. 1999; 103 : 11-21.