JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205

Volume 15 Issue 06, June 2025

Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

ALLELIC POLYMORPHISMS OF FOLATE CYCLE GENES AND THEIR IMPACT ON THE HEMOSTASIS SYSTEM

Kurbonova Zumrad Chutbayevna
Mirzamudova Nilufar Abdurashid kizi
Professor, Head of the Biomedical Technology Center
of the Tashkent State Medical University, DSc
1st year PhD student of the Tashkent State Medical University
**mirzamudova@mail.ru*

Abstract: Allelic polymorphisms in folate cycle genes, particularly in MTHFR (C677T and A1298C), MTR (A2756G), and MTRR (A66G), exert a significant influence on the function of the hemostasis system. These polymorphisms lead to elevated homocysteine levels, thereby increasing the risk of thrombogenesis. For instance, in individuals carrying the T allele of the MTHFR C677T polymorphism, reduced enzymatic activity results in hyperhomocysteinemia, which is associated with an increased risk of cardiovascular diseases and thromboembolic events

Keywords: folate cycle, allelic polymorphisms, MTHFR C677T, homocysteine,

hemostasis, thrombosis risk, metafolin, DNA methylation

Introduction. The hemostatic system is a complex, multi-stage mechanism that regulates blood coagulation processes. This system plays a crucial role in rapidly and effectively halting blood flow during vascular injury [2]. The main components of hemostasis — platelets and coagulation factors — work in coordination to stop bleeding [3]. A disruption in this balance may lead to either thrombosis or hemorrhage.

The folate cycle is essential for methylation processes, homocysteine metabolism, and the synthesis of S-adenosylmethionine (SAM) in the body. Vitamins such as folate, B12, B6, and B2 act as cofactors in these processes. Polymorphisms in folate cycle genes — including MTHFR, MTRR, and MTR — can alter folate and homocysteine levels, leading to dysfunction in the hemostasis system. These polymorphisms may weaken the body's protective mechanisms against thrombosis [4].

The folate cycle genes — namely MTHFR (methylenetetrahydrofolate reductase), MTR (methionine synthase), and MTRR (methionine synthase reductase) — play a key role in regulating homocysteine metabolism. Homocysteine is an amino acid whose elevated levels can damage vascular endothelium and lead to disruptions in the hemostasis system. High homocysteine levels also promote inflammation and oxidative stress, enhance platelet activation, and significantly increase the risk of thrombosis [5,6].

Numerous studies over the past decade have demonstrated that allelic polymorphisms in folate cycle genes — particularly MTHFR C677T and MTRR A66G — are associated with elevated

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homocysteine levels and dysfunction in the hemostasis system [7]. These genetic alterations slow homocysteine metabolism and disrupt hemostatic balance, resulting in an imbalance between coagulation and anticoagulation processes. Moreover, polymorphisms in folate cycle genes can influence the expression of coagulation factor genes and promote thrombin production, thereby significantly increasing the risk of arterial and venous thrombosis [8–10].

Folate cycle genes contribute to the regulation of hemostasis not only through homocysteine metabolism but also by affecting the gene expression of coagulation and anticoagulation factors. Studies show that polymorphisms in MTHFR, MTR, and MTRR can alter the functional state of the vascular endothelium, thereby influencing platelet activation and triggering the coagulation cascade [8]. Furthermore, polymorphisms related to the folate cycle can modify the expression of coagulation factors such as factor VII and factor VIII, affecting thrombin generation. This accelerates blood clotting and may disrupt the delicate balance of the hemostatic system [9].

Elevated levels of homocysteine induce oxidative stress and inflammation in the endothelial lining of blood vessels, which further influences the blood coagulation process. Under such stress conditions, platelets become more activated and adhesive, increasing the risk of thrombosis [10]. Along with increased homocysteine levels, genetic polymorphisms also contribute to the weakening of the blood's anticoagulant system. For example, alterations in folate cycle genes have been shown to negatively affect the production of anticoagulant proteins such as protein C. This complex gene-environment interaction, particularly considering homocysteine's role in hemostasis, is crucial for identifying individual genetic profiles and developing personalized therapeutic strategies [11,12].

From a clinical perspective, identifying allelic polymorphisms in folate cycle genes serves as an important biomarker for the etiology and prevention of thrombotic diseases. Monitoring homocysteine levels and conducting genetic testing play a key role in the development of personalized treatment strategies. Therefore, the study of polymorphisms in folate cycle genes is essential for understanding the complex mechanisms of the hemostatic system and for creating new diagnostic and therapeutic approaches [13].

Within the framework of personalized medicine, the identification of polymorphisms in folate cycle genes can assist in designing individualized treatment plans for patients. Supplementation with folate and vitamin B12, as well as therapies aimed at lowering homocysteine levels, have proven effective in reducing thrombosis risk in patients with these polymorphisms. Moreover, regular monitoring of homocysteine levels and genetic screening are considered critical for the prevention of cardiovascular diseases. Genetic testing, especially in high-risk patient groups, is employed for early diagnosis and preventive measures [14].

The MTHFR C677T polymorphism has been linked in numerous clinical studies to the development of arterial thrombosis, myocardial infarction, and stroke. This polymorphism significantly increases the risk of thrombotic events, particularly in individuals with elevated homocysteine levels. Similarly, the MTRR A66G polymorphism has been shown to contribute to hemostatic imbalance and abnormalities in the coagulation process [15].

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These findings highlight the significance of allelic polymorphisms in folate cycle genes not only at the molecular and biochemical levels but also from a clinical standpoint. They provide a foundation for developing new approaches in the diagnosis and treatment of thrombosis and coagulation disorders.

Conclusion. Allelic polymorphisms in folate cycle genes significantly impact the normal functioning of the hemostasis system. These genetic alterations increase homocysteine levels, disrupt coagulation and anticoagulation processes, and raise the risk of thrombosis. Therefore, identifying these polymorphisms is crucial for clinical diagnostics and personalized therapy. Ongoing research into these mechanisms contributes to the development of more effective therapeutic strategies.

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