Clinical Implications of *MTHFR* Gene Polymorphism in Various Diseases

Kaiser Jamil*

Genetics Department, Bhagwan Mahavir Medical Research Centre, Hyderabad, India

What prompted me to write this editorial was due to the fact that emerging bodies of in vitro and clinical evidence suggests that *MTHFR* SNPs may be important as pharmacogenetic determinants in predicting the response to toxicity of methotrexate and 5-fluorouracil-based cancer and anti-inflammatory treatments because of their well-defined and highly relevant biochemical effects on intracellular folate composition and one-carbon transfer reactions. *MTHFR* gene mutation has been related to many diseases including colon cancer, leukemia, vascular disease, depression, schizophrenia, migraine with aura, glaucoma, Down syndrome, and neural tube defects to name a few. Earlier Research performed during the past decade has clarified our understanding of *MTHFR* deficiencies that cause hyperhomocysteinemia with homocystinuria, or mild hyperhomocysteinemia. The involvement of *MTHFR* in disease was first published by Mudd et al. [1] who identified a patient with homocystinuria due to a severe deficiency of the enzyme. Recently, Tongboonchoo et al. [2] reported the association between *MTHFR* C677T polymorphism with osteoporosis in postmenopausal women. Osteoporosis and osteopenia is rising with the increase in numbers of postmenopausal women, and MTHFR, a homocysteine catabolizing enzyme, was found to be involved in the regulation of bone mineral density (BMD). Further, Zidan et al. [3] Demonstrated an association of *MTHFR* A1298C polymorphisms with congenital heart diseases (CHD) in Egyptian children and their mothers, while, *MTHFR* C677T polymorphisms were significantly associated with the risk of CHD in the children only, and an association between combined *MTHFR* A1298C and C677T polymorphisms and CHD was recorded in the children and their mothers. Also, homocysteine levels were significantly increased with both *MTHFR* 677TT and 1298CC genotypes in Egyptian children with CHD. The functional point mutation C677T in the *MTHFR* gene has been reported to contribute to hyperhomocysteinaemia which is a risk factor for atherothrombotic ischaemic strokes. TT genotypes of the MTHFR- C677T polymorphic gene was an important determinant for homocysteine levels in Malaysian ischaemic stroke patients [4].

A Russian study [5] observed that the *MTHFR* gene polymorphism correlated with an increased risk of migraine, particularly migraine with aura. The substitution of cytosine for thymine at the position 677 of the *MTHFR* gene leads to formation of the thermolabile form of the protein and development of hyperhomocysteinemia, which increases the probability of migraine. Yigit et al. [6] observed a high association between the *MTHFR* gene C677T mutation and diabetic neuropathy in the Turkish Population. In addition, they also reported that the history of retinopathy was associated with the *MTHFR* C677T mutation in patients with diabetic neuropathy. In this brief note I have attempted to highlight the complex role of the *MTHFR* gene mutations and its association with many diseases, summarizing the current state of knowledge on mutations/polymorphisms in *MTHFR* and discussed some of our own findings in leukemia and breast cancer.

MTHFR is highly polymorphic in the general population [7]. More precisely, the *MTHFR* gene is located from base pair 11,845,786 to base pair 11,866,159 (Cytogenetic Location: 1p36.3) on chromosome 1. It is expressed in various tissues including the brain, muscle, liver, and stomach [8]. *MTHFR* gene mutation can cause methylenetetrahydrofolate reductase deficiency. Two common mutations in the *MTHFR* gene interfere in the production of an enzyme that doesn't work as well as in normal. These "variants" are C677T and A1298C, the nucleotide 677 polymorphism results in an alanine to valine (C → T) substitution. The second common *MTHFR* polymorphism, a glutamate to alanine (A → C) change at position 1298, also influences the specific activity of the enzyme, homocysteine levels, and plasma folate concentration but to a lesser extent than the C677T polymorphism. Generally, it is believed that *MTHFR* SNPs are ideal candidates for investigating the role of SNPs in cancer risk modification and treatment. In fact, a huge expanse of molecular epidemiologic evidence indicates that the *MTHFR* 677 variant T allele is connected with the risk of developing cancer, in a site-specific manner [9]. Furthermore, changes in intracellular folate cofactors resulting from the *MTHFR* 677T variant may explain cancer risk modification associated with this variant. Because the *MTHFR* SNPs are prevalent, the pharmacogenetic role of the *MTHFR* SNPs has significant clinical implications since Methotrexate (MTX) [10] and 5-FluoroUracil (5FU) are widely used for the treatment of common cancers and inflammatory conditions [9]. It is certain that patients with *MTHFR* SNPs receiving chemo-regimen of these common drugs suffer severe adverse drug reactions. Our studies on SNPs in breast cancer and leukemia [11, 12] are good examples to relook at the role of these SNPs as biomarkers of disease susceptibility and their role in drug-gene interactions [13]. It is hypothesized that there may be a correlation between functional polymorphisms in the gene for the folate metabolizing enzyme, 5,10- methylenetetrahydrofolate reductase and leukemogenesis because of the association between folate status and susceptibility to genetic damage in dividing cells. *MTHFR* catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the major circulatory form of folate and carbon donor for the remethylation of homocysteine to methionine. A decrease in the activity of the *MTHFR* enzyme augments the pool of methylenetetrahydrofolate at the expense of the pool of methyltetrahydrofolate. This increase in availability of methyltetrahydrofolate in the DNA synthesis pathway lessens the misincorporation of uracil into DNA, which may otherwise lead to double-strand breaks during uracil excision repair. Some studies have shown that individuals with adequate folate status, who are homozygous for the *MTHFR* 677TT mutation, have a reduced incidence of colorectal cancer and leukemia. In our study, we examined the effect of *MTHFR* C677T and A1298C polymorphisms in Acute Lymphoblastic Leukemia (ALL).. Specifically, we found that individuals with at least one *MTHFR* mutation at 677CT or 1298AC were less likely

***Corresponding author:** Dr. Kaiser Jamil, Head, Genetics Department, Bhagwan Mahavir Medical Research Centre, 10-1-1, Mahavir Marg, AC Guards, Hyderabad-500004, India, Tel: +91- 9676872626; Fax: +91-9676872626, E-mail: kj.bmmrc@gmail.com

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to contract ALL [11]. Moreover, the possibility also existed that these variants may be influenced by the folate uptake of mothers during pregnancy, thereby influencing the enzyme activity and the ethnicity of the cases examined to date. DNA methylation plays an important role in the regulation of gene expression and maintenance of genomic stability. *MTHFR* is involved in DNA methylation and the availability of uridylates and thymidylates for the DNA biosynthesis and repair. Reduced *MTHFR* activity results in increased levels of cytosolic 5,10-methylenetetrahydrofolate, which may protect cells from DNA damage induced by uridylate misincorporation. Although the *MTHFR* 1298 polymorphism have not been studied as extensively, our results indicated a frequency of 32% for the C variant among controls were not too different to the values reported by Weisberg et al. [14] and Van der Put et al. [15]. It is also reassuring that the distributions of the polymorphic alleles within our control groups were slightly different, suggesting that the decreased risks observed for ALL are not a consequence of a peculiar polymorphic distribution among that specific control group. The single nucleotide polymorphism C677T have been found to be associated with decreased enzyme activity and plasma folate, and thus may play a crucial role in the etiology of several cancers. This decrease was reported in people with either high or low folate status. Previous studies have suggested that low folate intake was associated with increased risk of lung cancer. Our studies also show that deficient folate metabolism is associated with anemia in cancer patients [16]. *MTHFR* is one of the enzymes involved in folate metabolism and is thought to influence DNA methylation and nucleotide synthesis.

The cloning of the *MTHFR* coding sequence was initially followed by the identification of the first deleterious mutations in MTHFR, in patients with homocystinuria. Shortly thereafter, the 677C→T variant was identified and shown to encode a thermolabile enzyme with reduced activity [17]. Currently, a total of 34 rare but deleterious mutations in MTHFR, as well as a total of 9 common variants (polymorphisms) has been reported. The 677C→T (A222V) variants are particularly noteworthy since it has become recognized as the most common genetic cause of hyperhomocysteinemia. The disruption of homocysteine metabolism by this polymorphism influences risk for several complex disorders [7].

Wilson et al. [18] reported that high blood pressure (BP) and elevated homocysteine are independent risk factors for CVD and stroke in particular. The main genetic determinant of homocysteine concentrations is homozygosity (TT genotype) for the C677T polymorphism in the *MTHFR* gene, typically found in approximately 10% of Western populations. The enzyme 5,10-methylene-tetrahydrofolate reductase (MTHFR; EC 1.5.1.20) is linked to DNA methylation, synthesis, and repair. C677T is one of the most important polymorphisms in the *MTHFR* gene. Clinical implications of *MTHFR* mutations extend beyond cancer to cardiovascular diseases [19, 20]. Since hyperhomocysteinemia had emerged as a risk factor for cardiovascular disease, the 677C→T variant became an excellent candidate for risk modification of this complex trait; the initial studies supported this concept while subsequent studies reached different conclusions. A couple of reports also demonstrated elevated plasma total homocysteine in families with neural tube defects. Consequently, soon after its initial identification, the *MTHFR* variant was reported to be the first genetic risk factor for neural tube defects [21, 22]. The number of clinical conditions influenced by the 677 variant has grown considerably; the majority of the studies have used the initial *HinfI* digestion protocol for diagnosis of the variant.

There are no universal strategies to overcome drug resistance in cancer. Various efforts to deal with this problem relate to pharmacogenomics to be tailored to each patient. Oncoproteomics will play an important role in the development of personalised cancer therapy. Use of pharmacogenomic technologies in early clinical trials is enabling rapid assessment of the efficacy of anticancer agents, and reducing the time of drug development. Application of pharmacogenetics will reduce the adverse effect of anticancer drugs. Cell/gene therapies, cancer vaccines and RNA interference [23] will facilitate the development of personalised cancer therapy. Our earlier studies have shown the role of SNPs in drug metabolizing genes in breast cancer [24-27] and in head and neck cancers [28]. Further, our studies also highlight the importance of gene networking in understanding disease mechanisms [29-32].

Since the isolation of the cDNA in 1994, the work on the mammalian *MTHFR* gene has resulted in significant advances in our understanding of its genomic organization, genetic variations and involvement in human disorders [33]. Several important issues, however, remain to be addressed. Little is known about the regulation of this gene despite the fact that the enzyme links folate and homocysteine metabolism, and is involved in such critical cellular processes as DNA synthesis and DNA methylation. Investigations are required to understand the regulatory regions and their modulation, as well as the factors that affect alternative splicing and synthesis of the two protein isoforms. These are not easy tasks given the unusually complex *MTHFR* gene structure.

Although numerous clinical association studies have been performed on *MTHFR* variants, conclusions have been contradictory in some cases, due to the multifactorial nature of the disorders and our inability to identify the multiple genetic and environmental factors that can interact with *MTHFR* polymorphisms to impact disease risk. The biologic and tissue-specific impact of *MTHFR* deficiency has also not been adequately addressed since these types of investigations cannot be readily performed in human subjects; the availability of an animal model may be useful in this regard. To complete this editorial I have read about 200 articles on MTHFR, which I cannot list here but their views thoroughly match mine, hence, I have included some of my own studies on this gene along with other relevant references.

In the advancement of personalized medicine, diagnosis of the disease has entered the realm of genetic testing [34]. *MTHFR* gene mutations and other methylation dysfunction are a significant health issues affecting millions of people, however sadly this is largely ignored. At present there is great need for understanding the condition and a greater need for its management. I do believe that there is much to be learned as there is no universal magic bullet for its management the best therapy depends on the molecular features of the tumor.

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