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Methylene tetrahydrofolate reductase gene and coronary artery disease

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Hyperhomocysteinemia has been identified as a risk factor for coronary artery disease (CAD). In a nested case control study in Norway on 21,826 subjects in general population, hyperhomocysteinemia was clearly identified as an independent risk factor for CAD with no threshold level. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the methylation of homocysteine and its role in this pathway is outlined in Figure. Several inherited enzyme defects that can lead to elevated level of plasma homocysteine have been reported. Defective cystathionine b-synthase was the first to be extensively studied. However, defective remethylation of homocysteine due to defective MTHFR was another cause of hyperhomocysteinemia leading to premature vascular disease.

So far 10 mutations have been identified in the gene for MTHFR that result into decreased activity of this enzyme, which varies to a great extent. However, a homozygous mutation of the MTHFR gene (677C →T; ala val) alters the highly conserved amino acid alanine to valine, which results in compromised activity of MTHFR and leads to reduced methylation of homocysteine, and hence, to hyperhomocysteinemia. This variant of MTHFR had increased thermolability and was reported to be associated with the development of CAD. Since then the polymorphism of the gene of this enzyme has been a subject of great interest and a number of investigators have reported different results from a number of different populations.

The objective of this review is to highlight the results of some of these studies and to emphasize the need to focus on the genetic architecture of CAD in a country, such as, Pakistan where this disease is quite common in the younger population. As a general rule, the earlier the onset of a complex disease (which results from interactions between genetic and environmental factors), the greater the role of the genetic make-up.

Studies on MTHFR Polymorphism in Coronary Artery Disease

During the past 10 years, there have been a number of studies in all the continents on investigating the effect of MTHFR gene polymorphism on the development of CAD.
Table summarizes the results of these studies in terms of prevalence of MTHFR gene variants in CAD patients and normal healthy controls in different populations. In addition to these studies, polymorphism of MTHFR gene has also been recently reported in a Chinese population\textsuperscript{17} and in a Russian population in Western Siberia.\textsuperscript{18} Both of these studies indicated little or no correlation of MTHFR T677 allele with coronary heart disease. In a recent study by Nakata et al\textsuperscript{19}, it has been postulated that the Val allele of MTHFR increases the relative risk for thrombosis homocysteine levels, although a blood pressure attenuates the disease.

In a previous study by Kang et al., the prevalence of thermolabile MTHFR among CAD patients (n=212) compared to controls (n 202) was found to be statistically significant (17% vs 5% and $p^{15}$).

**Effect of MTHFR Mutation on Homocysteine**
In view of the above mentioned studies, it becomes quite evident that the frequency of homozygotes (TT) genotype varies among different populations. The overall effect of this mutation on homocysteine concentration in plasma depends on study design, inclusion criteria, ethnic background, age and vitamin intake of the population. With the exception of a few studies, most studies indicate an association of homozygous genotype (TI) with hyperhomocysteinemia. Since folate status is considered to be an important modulator of homocysteine level in homozygous individuals, it is possible that the different homocysteine levels in homozygotes (IT) reported in different studies may have been due to different intakes of folic acid by the study populations. Therefore, determination of folate level could be an important factor for studying the effect of genotype on homocysteine levels. Taken together, the facts that hyperhomocysteinemia is an established risk factor for the development of CAD and that reduced MTHFR activity is most commonly observed among IT homozygotes suggests that an association exits between the frequency of this genotype and risk of CAD.

**MTHFR Mutation and Risk of CAD**

A closer look at some of the studies would reveal that a stringent criteria for the selection of controls might be having a bearing on the outcome of that study. For example, Kang et al., who have reported a clear association between homozygotes for the variant enzyme and the development of CAD, recruited healthy controls with no history and clinical evidence of arterial occlusive disease. On the other hand, in a study by Kluijmans et al., that shows only a modest association, control subjects recruited from the general population possibly included some patients with a positive history of CAD. This might have diluted the effect of homozygous TI genotypes on the development of CAD. Although a number of studies have failed to show any association of homozygous TI genotypes with the risk of CAD, a meta-analysis on 8 different case-controlled studies on the thermolabile MTHFR variant in CAD indicated that the IT genotype is a modest risk factor for CAD.

**MTHFR Mutation and Age**

The low frequency of a genetic risk factor in a population can contribute to the population’s longevity. If the MTHFR C677T mutation is a risk factor for CAD, then its prevalence should be less in the older population. In a study by Matsushita et al., the frequency of homozygous MTHFR mutation in younger Japanese population (<54 years) was found to be 19% compared to 7% in the older group (<90 years). The difference was statistically significant especially among males (P= 0.006) indicating that this mutation varies with age in the normal population, and that younger people are at a greater risk of developing CAD in such a population. This trend was also observed by Faure-Delanf et al., who reported a decreased frequency of MTHFR mutated allele among French centenarians (age >100 yr; 13.3%) and nonagenarians (age >90 years; 11.4%) compared to controls (age 20 - 70 yr; 18.5%). Keeping this in view, it would be logical to assume that in studies involving older populations, the frequency of the variant gene would be low both in cases and controls and, therefore, any weak association of the variant allele with CAD would be masked. It is noteworthy that most studies showing an association between the MTHFR C677T mutation and CAD were on relatively younger populations. For example, an investigation on Turkish patients less than 45 years old reported a significant difference in the
frequency of the variant MTHFR amongst cases and controls. Another study reported a similar association on Polish patients who were less than 50 years of age. This notion requires further confirmation by carrying out studies on younger populations of patients.

**MTHFR Mutation, Folate Status and Risk of CAD**

Frostell et al have identified a region in the human dihydrofolate reductase gene that bears a homology with MTHFR. This region of MTHFR might also be involved in folate binding, and the enzyme may be stabilized in the presence of folate. Therefore, with better folate status, even variant MTHFR T677 may not be associated with hyperhomocysteinemia, suggesting that homozygous IT genotypes may not necessarily be associated with increased risk of CAD in individuals with high folate levels. This possibility has also been highlighted by van Bockxmeer et al. in their study on Western Australian population, as well as by Ma et al. in their study on well-nourished US physicians.

In a third world country like Pakistan, where folate deficiency is quite common and where CAD is quite prevalent in younger population, it would be important to determine the role of the MTHFR gene in the development of CAD. Such a study will not only be of significance in unraveling the genetic architecture of CAD in our population but may also provide an understanding of the role of folate deficiency (if any) in the development of CAD.

**References**

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