Relation between Methylene Tetrahydrofolate Reductase C677T Gene Polymorphism, Hyperhomocysteinemia and Coronary Artery Disease

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Abstract

Background and Aim: Hyperhomocysteinemia is known to be a risk factor for coronary artery disease (CAD). The most common form of genetic hyperhomocysteinemia results from the production of a variant of methylenetetrahydrofolate reductase (MTHFR) with reduced enzymatic activity. This study aimed to investigate the distribution of MTHFR genotypes in CAD patients and apparently healthy individuals and the role of this gene polymorphism as a risk factor for CAD and as a predictor of its severity.

Patients and Methods: The study included sixty CAD patients (27 with normal and 33 with abnormal coronary angiography) and thirty apparently healthy individuals as a control group after exclusion of smoking, hypertension, diabetes, thyroid dysfunction, dyslipidemia, and liver and kidney diseases. MTHFR genotyping was performed by PCR-RFLP. Measurement of serum homocysteine (Hcy) and folic acid (FA) levels were done for all patients and controls.

Results: Elevated Hcy levels were found in three apparently healthy persons so, they were excluded from the control group. There was significant elevation of Hcy level in CAD patients with abnormal angiography compared to control group (p<0.05). Lower frequency of CC genotype carriers was found in CAD patients groups in comparison with control group. CT genotype was detected in 33.4% of the control group, 33.3% of CAD patients with normal angiography and 57.6% of patients with abnormal angiography. Except for the three persons with high Hcy levels, no one of the apparently healthy subjects had TT genotype. However, this genotype was detected in 14.8% of CAD patients with normal angiography and 15.2% of patients with abnormal angiography. In CAD patients with abnormal angiography, TT genotype carriers had elevated Hcy levels compared to those carrying CC and CT genotypes (p<0.000). There was significant elevation of serum Hcy level in patients with stenosis 90% compared to those with stenosis >50-75% and 75-90%. However, there was insignificant difference in serum FA levels between all the studied groups with different classifications. Homozygous TT genotype was detected in all patients with one vessel affection and all patients with 90% stenosis. These patients had highly significant elevation of serum Hcy compared to CC and CT genotypes in the same respective group (p<0.000).

Conclusion: CC is the commonest genotype of MTHFR gene polymorphism in healthy individuals and patients with normal angiography and CT is the commonest one in those with abnormal angiography. TT genotype was associated with elevated homocysteine levels and so higher CAD risk. It is also associated with marked degree of stenosis in coronary vessels.

Key Words: Methylene tetrahydrofolate reductase — Hyperhomocysteinemia — Gene polymorphism — Coronary artery disease — Folic acid.

Introduction

CORONARY artery disease (CAD) is the leading cause of death in the high-income countries and the second cause in middle and low-income countries. Lifestyle and environmental factors play an important role in coronary artery disease development. In addition, family clustering suggests a genetic predisposition 111. Despite all the advances, the WHO reported that cardiovascular disease will remain as a world-wide health problem until 2030 [2]. It is well documented that the pathogenesis of vascular disease is multifactorial. Many risk factors have traditionally been associated with atherosclerosis e.g. hypertension, diabetes, chronic renal failure, and dyslipidemia, which have been coined conventional risk factors. Recently, the levels of these conventional risk factors in many cases have been within the biological reference interval. Hence it has become necessary to identify new risk factors 131.

Homocysteine (Hcy), an intermediary in the production of cysteine from methionine, is a non-essential sulfur-containing amino acid. Plasma Hcy level is affected by both genetic and environmental factors e.g. low consumption of folate, vitamin
B12 & B6, smoking and obesity [4]. A normal total plasma Hcy concentration ranges from 5 to 15μmol/L. Hyperhomocysteinemia is classified as follows: Mild (15-30μmol/L), intermediate (30-100μmol/L), and severe (>100μmol/L) [5]. Elevation of Hcy was reported in many conditions such as altered absorption or increased oxidative catabolism of serum folate, which correlates inversely with Hcy concentration in smoking [6], decreased excretion of Hcy in chronic renal failure [7], decrease hepatic levels of enzymes involved in the remethylation pathway of homocysteine (Hcy remethylates to methionine, thus, preventing the accumulation of homocysteine) caused by hyperhomocysteinemia [8] or chronic liver disease [9]. Increased homocysteine level can promote CAD by direct cytopathic effects on the endothelium, increased adhesiveness of the platelets and effects on clotting cascade [10].

The commonest form of genetic hyperhomocysteinemia includes several variants of enzymes involved in the homocysteine metabolic pathway such as methylenetetrahydrofolate reductase (MTHFR) [4]. The human MTHFR gene is mapped to the short arm of chromosome 1 (1p36.3). The gene consists of 11 exons and 10 introns [11]. Until now, more than 20 mutations of this gene have been identified, with the C677T mutation, which involves the change of alanine to valine, being the most common [12]. The 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate, and a co-substrate for homocysteine remethylation to methionine [13]. So, it contributes in maintaining circulating levels of folate and methionine, thus, preventing the accumulation of homocysteine [14]. There is much controversy about the relationship between MTHFR C677T gene polymorphism and CAD risk. Moreover, there is a geographical variation in the association of this polymorphism and coronary heart disease among different populations; in Europe, North America, Asia and the Middle East [15].

This work aimed to study the distribution of MTHFR genotypes in coronary artery disease patients and apparently healthy persons. We also aimed to reveal the role of this polymorphism in predisposition and severity of coronary artery disease in order to assess the benefit of genotyping in taking protective measures for carriers of the risky genotype.

**Patients and Methods**

This study included sixty CAD patients with history of acute coronary syndrome undergoing coronary angiography which was performed in the cardiac catheterization unit of Assiut University Hospital. Their ages ranged from 33-65 years including 50 males and 10 females. The study also included 30 age and sex matched apparently healthy subjects as a control group with age ranged from 35-55 years including 23 males and 7 females. Exclusion criteria included history of smoking, hypertension, DM, renal impairment, hypothyroidism, liver diseases and dyslipidemia. All participants were subjected to full medical history, clinical examination and ECG. Echocardiography and coronary angiography were done for patients only. According to angiographic findings CAD patients were classified into two groups: Twenty seven CAD patients with normal angiography, and thirty three CAD patients with abnormal angiography. An informed consent was obtained from all participants and the Ethical Committee of Assiut University Faculty of Medicine approved this study.

**Methods:**

Blood samples were withdrawn from all participants after 12-14 hours fasting and were divided into: Two ml into EDTA coated tube and frozen at —70°C for DNA extraction (for MTHFR genotyping). Six ml of blood was centrifuged for separation of serum and divided into aliquots for routine investigations (including serum glucose, kidney, liver & thyroid function tests and lipid profile), homocysteine and folic acid determination.

Serum homocysteine and folic acid levels were measured by chemiluminescent immunoassay using IMMULITE 1000 auto analyzer (a kit supplied by Siemens) and MAGLUMI auto analyzer (a kit supplied by SNIBE), respectively.

**Genotyping of MTHFR by PCR-RFLP technique:**

MTHFR genotyping was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). Genomic DNA was extracted from whole blood using QIAamp DNA Blood Mini kit based on protease digestion (QIAGEN, Germany) Amplification of target sequences was done by PuRe Taq Ready-To-Go PCR beads (supplied by GE Health Care) using specific primers: Forward primer with a sequence 5’CCTTG AACAGGTGGAGCCAG-3’ and reverse primer with a sequence 5’GGGCTGAGAT GGGGTGAG-3’. In addition to PCR bead, the reaction mixture consisted of 50ng of DNA and 50pmol of each primer. Thermal Cycling conditions included: one cycle of denaturation for 5min. at 95°C, thirty five cycles of: Denaturation (lmin. at 95°C), annealing (30 sec at 65°C) & extension (lmin. at 72°C), and one cycle of extension for 7min. at
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72°C according to the method described by Abu Amero et al., [16]. After PCR, the 294 by amplified product was digested by incubation for 5 min with the restriction enzyme "fast Hinfl" provided by (Thermo Scientific) which digest the product into 126,168bp only in the presence of T allele. The resulting digested fragments were separated by electrophoresis on 2% agarose gel and visualized under UV light after staining with ethidium bromide. The homozygous CC genotype resulted in a single fragment of 294bp, the heterozygous CT genotype produced 3 fragments 294,126,168bp, and the homozygous TT genotype resulted in 2 fragments of 126,168bp (Fig. 1).

Statistical analysis:

Data analysis was done using SPSS software version 17 (chicago, USA). The values were expressed as mean±SE. Statistical differences in laboratory variables between groups were assessed by Student’s t-test. Genotype frequency was expressed as number and percentage. Comparison of genotype frequency between groups was tested by Chi square test. Association between serum homocysteine level and severity of CAD was studied by Pearson’s correlation. The analyses or association were considered significant when p-value <0.05.

Results

Table (1) shows serum levels of Homocysteine (Hcy) and folic acid (FA) in the studied groups. In apparently healthy persons (30), three subjects had elevated Hcy levels (ranged from 33.9-50 with a mean value 44.6±SE 5.3gmol/L). So, they were excluded from the control group and considered a separate group. Serum Hcy levels showed significant elevation in CAD patients with abnormal angiography (p<0.05) and insignificant elevation in patients with normal angiography when compared to control group. Furthermore, patients with abnormal angiography had insignificant elevation of serum Hcy compared to those with normal angiography. The levels of serum FA didn’t show statistically significant difference in the studied groups when compared to each other.

The distribution of the MTHFR genotypes in the studied groups is shown in Table (2). Higher frequency of CC genotype was detected in control group (66.6%) compared to patient groups but, this difference was statistically significant only in patients with abnormal angiography (p<0.05). In addition, CAD patients with abnormal angiography had lower frequency of CC genotype than those with normal angiography (51.9% vs 27.2%, p<0.001). CT genotype was present in higher frequency in patients with abnormal angiography compared to controls (57.6% vs 33.4%, p<0.01) or compared to patients with normal angiography (57.6% vs 33.3%, p<0.05). TT genotype was detected in the three subjects who were excluded from the control group representing 10% of the whole group of apparently healthy subjects. No significant difference in the frequency of TT genotype was detected between patients with normal and abnormal angiography (14.8% vs 15.2%, p>0.05).

Table (1): Serum homocysteine and folic acid levels in CAD patients with normal coronary angiography and CAD patients with abnormal coronary angiography in comparison with control group (mean±SE).

<table>
<thead>
<tr>
<th>Groups</th>
<th>CAD with normal angiography (n=27)</th>
<th>CAD with abnormal angiography (n=33)</th>
<th>Control group (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (mmol/L)</td>
<td>15.4±1.7</td>
<td>18.7±1.8*</td>
<td>14.2±0.8</td>
</tr>
<tr>
<td>Folic Acid (ng/ml)</td>
<td>13.4±0.2</td>
<td>13±0.3</td>
<td>13.3±0.2</td>
</tr>
</tbody>
</table>

*p<0.05.

Table (2): Distribution of MTHFR genotypes in the studied groups.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CAD with normal angiography (n=27)</th>
<th>CAD with abnormal angiography (n=33)</th>
<th>Control group (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>14 (51.9%)</td>
<td>9 (27.2%)</td>
<td>18 (66.6%)</td>
</tr>
<tr>
<td>CT</td>
<td>9 (33.3%)</td>
<td>19 (57.6%)</td>
<td>9 (33.4%)</td>
</tr>
<tr>
<td>TT</td>
<td>4 (14.8%)</td>
<td>5 (15.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Data were presented as number and frequency (%).

Table (3) shows that; In CAD patients groups, TT genotype carriers had elevated Hcy levels when compared to CC and CT genotype carriers. This elevation was statistically significant only in patients with abnormal angiography (p<0.000). However, no statistical significant difference was found when comparing Hcy levels between CT and CC genotype carriers in both CAD patients groups. In control group, there was statistically significant elevation of serum Hcy level in carriers of CT genotype compared to carriers of CC genotype (p<0.05). In contrast, folic acid levels didn’t show statistically significant difference between carriers of different genotypes in all the studied groups. In order to reveal the relation between MTHFR polymorphism, Hcy levels and the severity of CAD, patients with abnormal angiography were further classified according to the number of vessels af-
fected and the degree of stenosis (numbers of patients and frequency are shown in Table 4). Serum levels of Hcy didn't show significant difference when comparing patients with different number of vessels affected. But, significant elevation of its level was found in patients with stenosis 90% compared to those of >50-75% stenosis and 75-90% stenosis. However, there was insignificant difference in serum FA between the groups with different number and degree of vessel affection.

Table (4) shows that TT genotype was detected in all patients with one vessel affection and all those with 90% vessel stenosis. These patients had highly significant elevation of serum homocysteine compared to CC and CT genotypes in the same group (p<0.000).

Moreover, studying the correlation coefficient of serum homocysteine level with severity of CAD showed significant positive correlation between serum homocysteine and degree of stenosis (r=0.314, p<0.05), Fig. (2). But, there was insignificant negative correlation between serum homocysteine and number of vessels affected (r=-0.158, p>0.05).

Table (3): Serum homocysteine and folic acid levels in different MTHFR genotypes in the studied groups (mean±SE).

<table>
<thead>
<tr>
<th>Genotype Groups</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAD with normal angiography:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hcy (timol/L)</td>
<td>14.3±1.6</td>
<td>13.1±1.6</td>
<td>24.2±9.1</td>
<td>CT vs CC, TT vs CC, TT vs CT</td>
</tr>
<tr>
<td>FA (ng/mL)</td>
<td>13.6±0.4</td>
<td>13.5±0.5</td>
<td>13.9±0.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CAD with abnormal angiography:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hcy (timol/L)</td>
<td>16.6±1.4</td>
<td>14.4±1.4</td>
<td>38.6±3.5</td>
<td>CC vs CT NS TT vs CC, CT &lt;0.000**</td>
</tr>
<tr>
<td>FA (ng/mL)</td>
<td>13.4±0.4</td>
<td>12.7±0.4</td>
<td>13.1±0.4</td>
<td>CT vs CC, TT vs CC, TT vs CT NS</td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hcy (timol/L)</td>
<td>13.1±1.0</td>
<td>16.4±1.3</td>
<td></td>
<td>CT vs CC &lt;0.05*</td>
</tr>
<tr>
<td>FA (ng/mL)</td>
<td>13.5±0.3</td>
<td>12.9±0.3</td>
<td></td>
<td>CT vs CC NS</td>
</tr>
</tbody>
</table>

* Significant. ** Highly significant. NS: Insignificant.

Table (4): Distribution of MTHFR genotypes in CAD patients with abnormal coronary angiography (n=33) according to number of vessels affected and degree of stenosis.

<table>
<thead>
<tr>
<th>Genotype severity</th>
<th>One vessel (n=19)</th>
<th>Two vessels (n=8)</th>
<th>Multi vessel affected (n=6)</th>
<th>&gt;50-75% stenosis (n=4)</th>
<th>75-90% stenosis (n=8)</th>
<th>90% stenosis (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Percent</td>
<td>(55.5%)</td>
<td>(44.5%)</td>
<td>(22.3%)</td>
<td>(33.3%)</td>
<td>(44.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>CT:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Percent</td>
<td>(47.4%)</td>
<td>(21%)</td>
<td>(31.6%)</td>
<td>(10.5%)</td>
<td>(26.3%)</td>
<td>(63.2%)</td>
</tr>
<tr>
<td><strong>TT:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Percent</td>
<td>(100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(100%)</td>
</tr>
</tbody>
</table>
Fig. (1): MTHFR genotypes determined by PCR/RFLP technique. Electrophoresis on agarose gel shows the digested fragments by HinfI restriction enzyme. The pattern shows MTHFR CC genotype (with fragment size 294bp) in position 1, 3, 4, 5, 8, 9, 12, 15, 16 & MTHFR CT genotype (with fragment sizes of 294, 168, 126bp) in position 2, 6, 7, 11, 13, 14 and MTHFR TT genotype (with fragment sizes of 168, 126bp) in position 10. The two sides of the figure demonstrates 50bp and 100bp DNA marker.

Fig. (2): Correlation between serum homocysteine level and degree of stenosis in CAD patients with abnormal angiography.

Discussion

Prevention of CAD has to be rooted on proper risk assessment reflecting ethnic variance [10]. Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thrombosis, and has been associated with other cardiovascular diseases such as coronary artery disease [13]. The mutation (C677T) of MTHFR gene results in a decrease in the enzyme activity that leads to mild hyperhomocysteinemia [17]. In this study, three out of thirty healthy persons (control group) had elevated Hcy levels and excluded from the control group and considered a separate group. Elevated levels of Hcy was found in CAD patients groups compared to control group. But, this elevation was statistically significant only in those with abnormal angiography. Hyperhomocysteinemia causes endothelial cell dysfunction and injury via production of potent reactive oxygen species. This metabolite is thrombogenic, as it increases thromboxane formation, antagonizes nitric oxide, enhances platelet aggregation, and inhibits protein C and thrombomodulin [18]. Elevation of Hcy in the studied patients is most probably due to genetic factors Hi, as we excluded other causes of elevation such as smoking [6], chronic renal failure [7], hypothyroidism [8] or chronic liver disease [9].

The most common form of genetic hyperhomocysteinemia results from the production of a thermolabile variant of methylenetetrahydrofolate reductase (MTHFR) with reduced enzymatic activity [15]. This polymorphism leads to mild hyperhomocysteinemia [19]. So, in this work we studied the distribution of MTHFR genotypes in CAD patients and apparently healthy individuals and the relation between this polymorphism and Hcy levels. In the control group, the CC genotype was detected in 66.6% and CT genotype in 33.4% of them. The three apparently healthy persons with elevated homocysteine levels had the homozygous TT genotype which represents 10% of the whole group of apparently healthy individuals. The frequency of MTHFR polymorphism in Turkish population was 61.9% for CC genotype, 30.5% for CT genotype and 7.6% for TT genotype [20]. But, in Lebanon population, it was 45.1% for CC genotype, 43.3% for CT genotype and 11.6% for TT genotype [21].

In the studied CAD patients with normal coronary angiography, the CC genotype represented 51.9%, CT genotype 33.3% and TT genotype 14.8%
of this group. The distribution of the genotype in CAD patients with normal coronary angiography in Morocco population was CC; 59.5%, CT; 32.1% and TT; 8.4% [22]. However, in Turkish population the MTHFR genotype distribution in the respective group was CC; 40.4%, CT; 45.2% and TT; 14.4% [24]. This discrepancy in genotype distribution between these studies and the present work could be attributed to different ethnic and geographical variations [21] and small sample size of the study.

Studying the relation between MTHFR gene polymorphism and Hcy levels reveals significant elevation of serum Hcy level in carriers of the CT genotype in the control group compared to carriers of the CC genotype. Moreover, in the studied CAD patients, elevation of homocysteine levels was found in TT genotype carriers compared to CC and CT genotype carriers. But, this elevation was statistically significant only in patients with abnormal angiography. It has been shown that a polymorphism of the MTHFR gene in individuals with the TT genotype leads to reduced enzyme activity and increased Hcy level [25]. Decrease enzyme activity in mutated form of enzyme may be due to weak binding affinity for the flavin cofactor, flavin adenine dinucleotide (FAD), when the protein contains valine instead of alanine at position 677 of the mutant gene. Valine containing enzyme easily loses its flavin cofactor in conditions of low riboflavin or low folate, causing the biologically active form of the enzyme to break down into inactive form. However, the presence of high folate concentrations could stabilize FAD binding and preserve enzyme functionality. These effects could be modulated by S-adenosyl methionine, indicating that riboflavin, folate, and methionine would all be important for maintenance of MTHFR activity in individuals with the variant enzyme [26].

Studying the relation between MTHFR gene polymorphism, homocysteine level and the severity of CAD revealed significant elevation of the Hcy level in CAD patients with 90% stenosis compared to 75-90% and 50-75% stenosis. There was statistically significant positive correlation between serum homocysteine and degree of stenosis. But, no significant difference was found in Hcy levels in patients with different number of vessels affected. On other hand, TT genotype was detected only in patients with single vessel disease representing 100% and only in patients with 90% stenosis representing 100%. These patients had highly significant elevation of serum homocysteine compared to CC and CT genotype carriers in the same group. The frequency of TT mutation was associated with the severity of stenotic lesions and the number of stenotic coronary arteries, suggesting that this mutation is closely associated with the severity of CAD [22]. Thermolabile MTHFR was found to be the cause of abnormal Hcy metabolism as it has reduced activity 70% in TT genotype and 35% reduced activity in CT genotype carriers and was also correlated to the severity of coronary syndrome. Although the exact mechanism of Hcy toxicity is unknown, it is believed that Hcy or its metabolite adversely affects vascular endothelium inducing atherosclerosis. Hcy is converted by methionyl-transfer RNA synthetase to Hcy thiolactone, which then reacts with lysine residues in proteins, damaging their structure and impairing their physiological activities [20].

However, there is much controversy about the relationship between MTHFR C677T1 gene polymorphism and CAD risk. This difference may be due to sample size, age group, and finally the influence of environmental factors [27]. For example, the MTHFR polymorphism is apparently a weaker predictor of coronary heart disease in American than in European populations, and this might be explained by mandatory B vitamin fortification of food items in the United States, which predictably increases the dietary intake of riboflavin and folate [28].

In the present study, the level of folic acid had no significant difference between patients and control groups. Moreover, there was no difference in serum folic acid in different MTHFR genotypes in all groups. Riboflavin is an important determinant of Hcy among individuals with the TT genotype who had normal folate level. It was reported that a genotype-specific response of Hcy to riboflavin supplementation confirm that riboflavin is an independent modifier of Hcy in individuals with the TT genotype. It could be predicted that individuals with the TT genotype who also have low riboflavin status would have an excess risk of heart disease, whereas with optimal riboflavin status, they would not carry the expected risk [29]. There is a possible contribution of plasma pyridoxal phosphate concentration, (PLP or vitamin B6) to hyperhomocysteinemia and vascular disease; low PLP levels were observed in individuals with the homozygote TT.
Recommendations:

- MTHFR genotyping should be included in routine risk assessment to detect CT and TT genotype carriers who need protective measures as physical care (avoids smoking and obesity), regular physical activity, and a healthy diet. Vitamin B supplementation has a major role in reducing Hcy levels in patients of CAD irrespective of the cause [31]. On other hand, Zappacosta et al., [32] reported that the supplementation with natural folate rich food, folic acid and 5-MTHF in Mediterranean population lead to reduction of Hcy concentration.

In conclusion, CC is the commonest genotype of MTHFR gene polymorphism in healthy individuals and patients with normal angiography and CT is the commonest one in those with abnormal angiography. TT genotype was associated with elevated homocysteine levels and so higher CAD risk. It is also associated with marked degree of stenosis in coronary vessels.

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