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5, 10-Methylenetetrahydrofolate Reductase (MTHFR) 677 C→T Genetic Polymorphism in 228 Croatian Volunteers

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A B S T R A C T

5, 10-Methylenetetrahydrofolate Reductase (MTHFR) is one of the key enzymes in the metabolism of homocysteine, where it catalyses its remethylation. The autosomal recessive bp 677 C→T mutation in the MTHFR gene leads to the substitution of valine for alanine. Individuals who are homozygous for this C677T mutation exhibit a decreased specific activity and increased thermolability of this enzyme. This leads to increased plasma levels of homocysteine, which is a known risk factor for atherosclerosis and various manifestations of the atherosclerotic disease. The aim of this study was to find out the distribution and frequency of this mutation in the general Croatian population. A group of 228 volunteers (175 males and 53 females) has been analyzed for the MTHFR polymorphism, which revealed the following distribution: 105 (46.05%) individuals were without mutation (C/C), 102 (44.74%) were heterozygous (C/T) and 21 (9.21%) homozygous (T/T). These findings are within the results of studies on other European populations.

***Key words**: MTHFR, 5, 10-Methylentetrahydropholate reductase, homocistein, C677T, atherosclerosis, Croatia.*

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Introduction

Homocysteine was first discovered by Butz and du Vigneaud in 1932 as an intermediary in methionine metabolism[1–3]. Thirty years later, its excretion in the urine of mentally retarded children was reported[4]. Subsequent studies of children with homocystinuria showed the association of greatly elevated blood homocysteine with premature arteriosclerosis and thromboembolic phenomena resulting in myocardial infarction, stroke, and early death. McCully established in 1969 a link between elevated plasma homocysteine concentrations and vascular disease[5,6]. Moderate hyperhomocysteinemia has also been associated with premature cardiovascular disease in adults lacking the mental and skeletal characteristics of homocystinuric children[7–12]. The role of elevated total homocysteine levels as a risk for arteriosclerotic vascular disease has attracted grow- ing interest since about half of all deaths are due to cardiovascular disease and its complications.

Homocysteine is an aminoacid intermediate produced during metabolism of the essential amino acid methionine. It may be metabolized in one of two pathways: remethylation back into methionine or transulphuration to cystathionine, which is converted into cystein, and ultimately, excreted in the urine (Figure 1).

Elevation in plasma homocysteine is typically caused by either genetic defects in the enzymes involved in homocysteine metabolism or by nutritional deficiencies of vitamin cofactors. The normal blood level of homocysteine is controlled by enzymatic conversion of the homocysteine to »methionine« or »cystathione«. These reactions are dependent upon 3 key enzymes and the vitamin cofactors B12, B6 and folic acid.

1. »Cystathionine b synthase« (requires vitamin B6 as a cofactor) converts homocysteine to cystathionine.

2. »5, 10-Methylenetetrahydrofolate reductase« or MTHFR (requires folate and B12 as co-factors) converts 5, 10 MTHF to 5-MTHF. The C677T mutation in the gene encoding MTHFR causes elevated levels of homocysteine. Since this path requires folic acid and vitamin B12 as cofactors, supplemented high intake of vitamins B12 and folate can normalize the otherwise elevated homocysteine.

3. »Methionine synthase«, (requires folate and B12 as co-factors) combines homocysteine with the 5-MTHF produced in the previous reaction. The homocysteine becomes »methionine« and the 5-MTHF

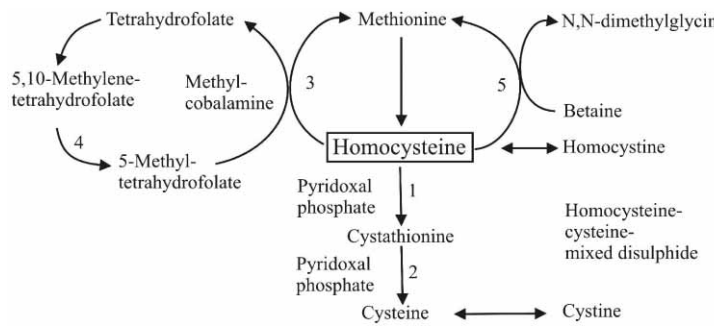

Fig. 1. Methionine metabolism. 1. Cystathionine synthase 2. γ-Cystathionase 3. N5-Methyltetrahydrofolate-homocysteine methyltransferase 4. 5,10-Methylene-tetrahydrofolate reductase 5. Betaine-homocysteine methylentransferase

becomes plain MTHF, which is converted back to 5, 10-MTHF to re-enter the cycle. The methionine then converts to 5-adenosylmethionine.

Methylenetetrahydrofolate Reductase (MTHFR) is an enzyme that catalyses the conversion of folate into a form that can help change homocysteine to methionine. The 2.2 kilobase long MTHFR gene is mapped to chromosome 1 at region 1p36.3. A MTHFR variant with reduced activity was described in 1988 by Kang et al.[13]. Frosst et al. identified the mutation responsible for this MTHFR variant: a cytosine to thymidine transition at nucleotide 677 (C677T) in the MTHFR gene[14]. This mutation results in a substitution of alanine to valine at position 226 in the MTHFR. The encoded protein has a 50–60% reduced enzymatic activity at 37degrees Celsius and higher, hence the term »thermolabile«.

Many studies have shown that homozygous (T/T) mutant subjects had significantly elevated plasma total homocysteine concentrations, whereas the total homocysteine concentration in heterozygous (C/T) individuals and in subjects with no mutation (C/C) was indistinguishable[14–18]. Other studies have shown that heterozygous (C/T) individuals had slightly elevated homocysteine levels in comparison to the homozygous wild (C/C) genotype[19].

The discovery of this mutation was of interest because elevated total homocysteine is associated with an increased vascular disease risk. Furthermore, some inverse associations between the TT mutations and gastric and proximal colon cancer have been established[20,21], as well as an increased risk for some severe neural tube defects such as spina bifida and anencephaly[22–24].

Another common mutation in the MTHFR gene is an adenine to cytosine transition at nucleotide 1298 (A1298C). Neither homozygosity nor heterozygosity of this mutation is associated with high plasma homocysteine levels or lower plasma folate concentrations. However, individuals who were heterozygous for both C677T and A1298C had a lower MTHFR activity of 41% of the control activity, as compared with individuals with a heterozygous C677T mutation alone or A1298C mutation alone that had a 45% and 68% respectively [25].

Subjects and Methods

Two hundred twenty-eight randomly selected blood donors were analyzed for the MTHFR gene polymorphism. The subjects were informed of the purpose of the study and signed a written consent, which had previously been approved by the Ethical Committee. They also filled out an uncomplicated questionnaire providing data about age, gender, vitamin intake and meat consummation prior to blood donation.

Venous blood was obtained by puncture of the cubital vein, collected in EDTA and immediately centrifuged at 2500 rpm for 10 min at 4 °C. Cells were kept at –30 °C until the genetic analysis was performed. The MTHFR C677T mutation was assessed using the Lightcycler-MTHFR C677 mutation detection protocol. The mutation detection protocol was adopted for the high-speed PCR in glass capillaries using the Lightcycler Instrument and hybridization probes for the genotyping of the C677T point mutation in exon 4 of the MTHFR gene. A 233 bp fragment of the MTHFR gene was amplified from genomic DNA using specific primers and the PCR product was detected by fluoresceine (Lightcycler-Red 640) using a MTHFR specific pair of hybridization probes. The following primers and probe were used: the forward primer was MTHFR-for, 5'-TGA AGG AGA AGG TGT CTG CGG G A-3'; the reverse primer was MTHFR-rev, 5'-AGG ACG GTG CGG TGA GAG TG-3'; and MTHFR-probe: 5'- AGC

TGC GTG ATG ATG AAA TCG GCT CC-3'-FLU. The underlined T indicates the position of a thymidine amino modifier to which the LC-Red640 dye is linked, and FLU indicates the 3' fluorescein.

The gender distribution of the 228 examined subjects was as follows: 175 males (76.75 %) and 53 (23.25 %) females. Our study group was randomly selected from healthy individuals- blood donors, which explains this male predominance in our study. The average age of the male studied individuals was 38.86 (range 19 to 64) and 37.06 (range 19 to 60) for females.

Results

These 228 individuals were analyzed and the distribution of the MTHFR genetic polymorphism was determined: 105 (46.05%) individuals were homozygous for the wild type (C/C), 102 (44.74%) were heterozygous (C/T) and 21 (9.21%) were homozygous for the mutation (T/T). (Table 1)

The distribution of the MTHFR polymorphism was also analyzed separately in relation to gender. The distribution of the MTHFR genotype variants in males was: 78 (44.57%) individuals had the wild homozygous (C/C) genotype, 79 (45.14%) were heterozygous and 18 (10.29%) had the mutant homozygous genotype (Table 1).

Among the 53 female individuals the distribution was as follows: 27 (50.94%) had the C/C genotype, 23 (43.39%) were heterozygous and 3 (5.66%) were T/T homozygous.

These results were compared with studies on various ethnic groups worldwide. Table 2 demonstrates the MTHFR C677T polymorphism in Croatians and comparison with some other European nations.

Discussion

Hyperhomocysteinemia is assumed to be an independent risk factor for cardiovascular disease and is thought to be responsible for about 10 percent of total risk[10,26].

Normal levels of fasting plasma homocysteine fall between 5 and 15 μmol/L. Moderate hyperhomocysteinemia refers to concentrations between 16 and 30, intermediate between 31 and 100, and severe hyperhomocysteinemia >100 μmol/L. Moderately elevated plasma homocysteine levels (>~15 μmol/L) are considered cytotoxic and are found in 5–10 percent of the general population and in up to 40 percent of patients with vascular disease [6,7,27–29]. Additional risk factors (smoking, arterial hypertension, diabetes, and hyperlipidemia) may additively or, by interacting with homocysteine, synergistically increase overall risk. Hyperhomocysteinemia is associated with alterations in vascular morphology, loss of endothelial antithrombotic function, and induction of a procoagulant environment[30–33]. Furthermore, special importance of the role of MTHFR C677T mutation and hyperhomocysteinemia lies in the new awareness that it also represents a risk factor for development of arterial and venous thrombosis[34].

Most known forms of damage or injury are due to homocysteine-mediated oxidative stress. Numerous agents, such as drugs, disease and life style factors also have an impact on homocysteine metabolism, when acting as direct or indirect antagonists of cofactors and enzyme activities.

The distribution of C677T allele is strikingly variable among different ethnic and racial groups[15,35–58]. Pooled data from various European studies that included about 7000 individuals showed that the C677T allele frequency appears to be high in Italy – 44%, 35% in Britain, 32 % in Ireland and 28 % in Norway. The allele frequency among whites from Australia, Brazil, Canada and the United States ranged from 34 to 37 percent.

TABLE 1
DISTRIBUTION OF THE C677T ALLELE OF THE MTHFR GENE IN 228 CROATIAN VOLUNTEERS

Gender	Number	Genotype			Allele frequency (%)		Frequency of TT homozygosity (%)		Frequency of CT (%)		Frequency of CC (%) homozygosity	
		TT	CT	CC	Frequency	95% confidence interval	Frequency	95% confidence interval	Frequency	95% confidence interval	Frequency	95% confidence interval
Male	175	18	79	78	32.9	27.9, 37.8	10.3	5.8, 14.8	45.1	37.8, 52.5	44.6	37.2, 51.9
Female	53	3	23	27	27.4	18.9, 35.9	5.7	*	43.4	30.1, 56.7	50.9	37.5, 64.4
Total	228	21	102	105	31.6	27.3, 35.9	9.2	5.4, 13.0	44.7	38.3, 51.2	46.1	39.6, 52.5

* Could not be assessed due to small sample

TABLE 2
DISTRIBUTION OF THE C677T ALLELE OF THE MTHFR GENE IN VARIOUS EUROPEAN POPULATIONS

Country	Total number	Genotype			Allele frequency (%)		Frequency of homozygosity (%)	
	Total	TT	CT	CC	frequency	95% confidence interval	Frequency	95% confidence interval
Britain/Wales *	1046	138	465	443	35.4	33.3, 37.4	13.2	11.1, 15.2
Croatia	228	21	102	105	31.6	27.3, 35.9	9.2	5.4, 13.0
France	133	13	70	50	36.1	30.1, 41.7	9.8	4.7, 14.8
Germany*	257	20	86	151	24.5	20.7, 28.1	7.8	4.5, 11.1
Ireland and Northern Ireland*	1309	141	568	600	32.5	30.7, 34.2	10.8	9.1, 12.5
Italy*	2053	370	1057	626	43.8	42.2, 45.3	18.0	16.4, 19.7
The Netherlands	503	45	234	224	32.2	29.3, 35.0	8.9	6.5, 11.4
Norway*	391	37	145	209	28.0	24.8, 31.1	9.5	5.0, 15.6
Sweden	126	13	50	63	30.2	24.3, 35.6	10.3	5.0, 15.6

*Pooled data from two or more studies.

The C677T allele frequency is low in some samples of individuals from sub-Saharan Africa (7 percent) and individuals of African descent living outside of Africa, being 5 % among Brazilian blacks, to 24% among members of one group of African-Americans in the United States.

The majority of studies of Asians were done on Japanese people where the C677T allele frequency is 35 percent%. Concerning Hispanics individuals, a Californian study on 169 whites of Hispanic origin, the allele frequency was 42%, being equally high as in a group of Colombians. The C677T allele frequency in Amerindians was also variable: it was high in a group of Cayapa Amerindians from Ecuador (43%) and in a group of Brazilian Amerindians (45%) and low in members of the Tupi Parakana tribe (11%).

The frequency of C677T homozygotes follows a similar pattern. Countries in which the frequency of C677T allele was highest also had the highest frequency of C677T homozygotes – the frequencies of C677T homozygotes reached 18 % in Italy but no T/T homozygotes were found in the group of 89 sub-Saharan Africans. A study on 250 healthy Mexican women demonstrated a 34.8% frequency of the TT genotype.

According to the Consensus Paper on the Rational Clinical Use of Homocysteine, Folic Acid and B-vitamins in Cardiovascular and Thrombotic Diseases-Guidelines and Recommendations, 5–15% of the German, Swiss and Austrian general populations were homozygous for the TT mutation. A meta-analysis of different groups of Europeans determined a mean prevalence of 9.2% of homozygotes for the mutation.

Our study of 228 subjects of the Croatian population, as presented in Table 1, showed that the distribution of the C677T polymorphism of the MTHFR gene was as follows: 46.05% individuals were homozygous for the wild type (C/C), 44.74% were heterozygous (C/T) and 9.21% were homozygous for the mutation (T/T). These findings are compared with other European nations in Table 2.

Conclusion

The true role of mild elevation of homocysteine, which results from the homozygous C677T mutation of the MTHFR gene, in the genesis of cardiovascular disease, remains still somewhat controversial: The opinion is divided whereas this mild homocysteinaemia may be considered an important risk factor in pathogenesis of atherosclerotic disease or if it only represents a marker for increased risk. The contribution of low folate levels in homocysteinaemia in individuals who are homozygous for the T/T genotype is unquestionable; dietary folate supplementation may be recommended in these individuals as a strategy in normalizing the levels of homocysteine and preventing atherosclerotic and peripheral vascular disease.

The distribution of MTHFR gene polymorphism in the studied Croatian population was as follows: approximately 46 % were homozygous for the wild type (C/C), 45 % were heterozygous (C/T) and 9 % were homozygous for the mutation (T/T); these numbers fall within the average findings of the Caucasian European population. These numbers may also be the foundation to a future preventive strategy in cardiovascular disease as well as guidance in treatment.

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5, 10-METILENTETRAHIDROFOLAT REDUKTAZA (MTHFR) 677 C→T GENSKI POLIMORFIZAM U 228 HRVATSKIH DOBROVOLJACA

S A Ž E T A K

5, 10-Metilentetrahidrofolat reduktaza (MTHFR) jedan je od ključnih enzima u metabolizmu homocisteina gdje katalizira njegovu remetilaciju. Autosomno recesivna mutacija 677. para baze C→T dovodi do zamjene valina alaninom. Osobe koje su homozigoti za ovu C677T mutaciju MTHFR gena imaju smanjenu specifičnu aktivnost i povećanu termolabilnost enzima. Ovo dovodi do povišenih razina homocisteina, a što je dobro poznati faktor rizika ateroskleroze te raznih manifestacija aterosklerotske bolesti. Cilj ove studije bio je otkriti distribuciju i učestalost ove mutacije u općoj hrvatskoj populaciji. Skupina od 228 dobrovoljaca (175 muških i 53 ženskih) analizirana je za MTHFR polimorfizam, te je otkrivena sljedeća distribucija: 105 (46.05%) osoba bilo je bez mutacije (C/C), 102 (44.74%) bili su heterozigoti (C/T) a 21 (9.21%) bili su homozigoti (T/T). Ovi nalazi odgovaraju rezultatima studija u drugim Europskim populacijama.