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Correlation of Homocysteine Metabolic Enzymes Gene Polymorphism and Mild Cognitive Impairment in the Xinjiang Uygur Population

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Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the genetic polymorphisms in the homocysteine (HCY) metabolic enzymes in the Xinjiang Uygur population who have mild cognitive impairment (MCI).

Material/Methods: Based on the epidemiological investigation, 129 cases of diagnosed Uygur MCI patients and a matched control group with 131 cases were enrolled for analyzing the association between the polymorphisms in the HCY metabolism related genes (C677T, A1298C, and G1968A polymorphisms in *MTHFR*, as well as the A2756G polymorphism in *MS*) and MCI by using the SNaPshot method. We then determined the homocysteine level in patients.

Results: In Xinjiang Uygur subjects, the A1298C polymorphisms in *MTHFR* and the A2756G polymorphisms in the MS gene in the MCI group were different from those in the control group. However, the C677T and G1968A polymorphisms in the *MTHFR* gene in MCI patients were not different from those in the control group. Multivariate logistic regression showed that, in addition to the well-known risk factors, such as low education level, high cholesterol level, high level of low-density lipoprotein, and high homocysteine levels, the A>G mutation in the MS gene at the rs1805087 locus was another independent risk factor for MCI in the Uyghur MCI population. The risk of MCI in G allele carriers was 2.265 times higher than that in matched control individuals (*95% CI: 1.205~4.256, P<0.05*).

Conclusions: The genetic polymorphism of HCY metabolizing enzymes is correlated to the occurrence of MCI in the Xinjiang Uygur population. The A2756G polymorphism in the MS gene could be an independent risk factor for MCI in the Xinjiang Uygur population.

MeSH Keywords: Homocysteine • Methionine • Mild Cognitive Impairment

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Background

Homocysteine (HCY), a sulfur-containing amino acid, is a precursor of methionine, cysteine, and glutathione. High homocysteine (HHCY) is a risk factor for impairment of cognitive function. In an epidemiological investigation of non-Alzheimer cognitive impairment in an elderly population, an increased HCY level was showed to be closely correlated to cognitive damage, increased risk of cognitive decline, and the progression to dementia [1]. Our previous study on the relationship between HCY and mild cognitive impairment (MCI) has shown that the plasma HCY level was correlated with the occurrence of MCI in the elderly in Xinjiang Uygur and Han ethnic regions, and that the plasma HCY level in MCI patients increased with age, indicating that HHCY is an important independent risk factor for MCI in the Uygur and Han populations in Xinjiang [2].

Based on our previous MCI epidemiological investigation, which utilized the case-control comparative method, the etiological relationship between MCI and the common mutations in HCY metabolic enzyme genes (including polymorphisms of C677T, A1298C, and G1968A in methylene tetrahydrofolate reductase (MTHFR) gene, and polymorphism A2756G in the methionine synthetase (MS) gene) was determined in order to build a genetic basis for the MCI etiology study.

Material and Methods

Objects

An MCI epidemiological investigation was carried out from August to October of 2010. A stratified, random, multistage cluster sampling approach was used to investigate 3346 Uygur residents aged 55 years old or older in Hetian, Xinjiang province.

Patient group

Patient selection was based on the epidemiological investigation and referred to the diagnostic criteria for MCI of the United States Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders revision IV (DSM-IV). One hundred and twenty-nine Uygur patients with MCI (74 males and 55 females) that had complete essential information, such as biochemical indexes and other basic diagnoses, were used as the experimental group. The average age of the patients in this group was 64.3±6.42 year. The exclusion criteria were: 1) history of mental illness or congenital mental retardation; 2) presence of severe heart, lung, liver, or kidney dysfunction, severe endocrine disorders, severe infectious diseases, or toxic encephalopathy; 3) neurological disorders which can cause brain dysfunction, such as stroke, Parkinson's disease, and brain tumors; 4 depression; 5) a history of head trauma, or special medication usage; and 6) alcohol-or drug-dependent in the past 6 months.

Control group

After a strict examination in the unrelated non-cognitive impairment elderly population, we selected 131 cases (75 males and 56 females) for inclusion in the MCI patient group, matched for gender, age, ethnic group, place of residence, educational background, and previous medical history. The average age in the control group was 64.4±6.45 year old.

All participants signed written consent forms and were examined. The study was approved by the Xinjiang Medical University Medical Research Ethics Committee.

Methods

Determination of biochemical indexes

Five ml of venous blood was taken from each subject in the morning after fasting for 12 hours. The biochemical indexes, including triglycerides (TG), total cholesterol (TC), glucose (GLU), and HCY, were measured using an automatic biochemical analyzer (Beckman, United States)

DNA Extraction

Genomic DNA was extracted from the venous blood samples treated with ethylene diamine tetraacetic acid (EDTA) anticoagulant by using the Whole Blood Genomic Extraction Kit (Tiangen, China) according to the manual.***Multiplex PCR amplification***

The primers used for the amplifications of the *MTHFR* (polymorphisms C677T, A1298C, and G1968A), and *MS* genes (polymorphism A2756G) were designed using Primer3 software (*http://Frodo.wi.mit.edu/*), and synthesized by Shanghai Shenggon Biological Technology Co. Ltd. The primer sequences were as follows: for the rs1801131 locus: forward primer 5'-GGATGAACCAGGGTCCCCACT-3', reverse primer 5'-GAAGAGC AAGTCCCCCA AGGAG-3', with a product of 159 bp. For the rs1801133 locus: forward primer 5'-GCCTCAAAGAAAAGCTG CGTG AT-3', reverse primers 5'-CCCAGTCCCTGTGGTCTCTTCA-3', with a product of 191 bp. For the rs1805087 locus: forward primer 5'-TGGCTATCTTGCATTTTCAGTGTTCC-3', reverse primers 5'-TCC AAAGCCTTTTACACTCCTCAAA-3', with a product of 229 bp. For the rs2274976 locus: forward primer 5'-TT GTCAGGTGGGGGAGTGGA-3', reverse primer 5'-GAGGCYTT TGCCCT GTGGA-3', with a product of 346 bp. The multiplex PCR reaction system (20 µl) included GC Buffer I, 3.0 mM Mg2+, 0.3 mM dNTP, 1 U HotStartTaq polymerase (Qiagen Inc. USA), 1 µl sample DNA, and 2 µl of multiplex PCR Primers (1 uM). The PCR cycling program was as follows: 95°C, 120 seconds;

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Table 1. General biochemical indexes of subjects.

	MCI group	Control group	t/χ^2	*P*
Numbe (n)	129	131		
Age (yr)	64.32±6.42	64.41±6.46	0.118	0.906
Gender (male/female)	74/55	75/55	0.00	0.985
ED	94/129	88/131	1.003	0.317
BMI (kg/m^2)	24.67±4.23	23.96±4.10	1.377	0.170
EH	47/129	40/131	1.016	0.313
DM	9/129	9/131	0.001	0.973
SBP (mmHg)	140.72±24.07	133.49±24.21	2.416	0.016
DBP (mmHg)	80.69±12.90	78.07±13.10	1.625	0.105
GLU (mmol/l)	6.03±2.96	5.47±1.81	1.829	0.069
TG (mmol/l)	2.99±1.39	2.04±1.26	5.832	0.000
TC (mmol/l)	4.70±0.87	4.50±1.02	1.751	0.081
HDL-C (mmol/l)	1.06±0.26	1.10±0.45	0.878	0.381
LDL-C (mmol/l)	2.77±0.73	2.40±0.61	4.355	0.000
Hcy (umol/l)	17.16±7.70	13.44±3.49	5.032	0.000

(94°C, 20 seconds; 65°C, 40 seconds (0.5°C lower stepwise), 72°C, 90 seconds, 11 cycles); (94°C, 20 seconds, 59°C, 30 seconds, 72°C, 90 seconds, 24 cycles); 72°C, 120 seconds.

PCR product purification

After amplification, 15 ul of PCR product was incubated with 5 U of SAP enzyme and 2 U of exonuclease I at 37 °C for 1 hour. The enzymes were inactivated by incubation at 75°C for 15 minutes.

SNaPshot extension reaction

The SNaPshot extension primers were designed such that the 3' end of the primer was located at the first base upstream of the polymorphic locus. The 5' end of the primer contained different lengths of polyT, so that the length of the product could be in the 20-50 bp range to facilitate detection. The extension primers were as follows: rs1801131SR: 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGG AGGAGC TGACCAGYGAAG-3'; rs1801133SF: 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTGCTGCGTGATGATGAAATYG-3'; rs1805087SF: 5'-TTTTTTTTTCATGGAAGAATATGAAG ATATTAG ACAGG-3'; rs2274976SR: 5'-TTTTTTTGCCCTGTGGATTGAGC-3'. The single-nucleotide extension reaction system (10 µl) contained 5 µl of the SNaPshot mixed solution (ABI), 2 µl of the PCR product after purification, 1 µl extension primer mixture (final concentration 1.0 µm), and 2 µl ultrapure water. The recycling program was as follows: 96°C, 1minute, 96°C, 10 seconds, 52°C, 5 seconds, 60°C, 30 seconds, 28 cycles. Finally, 1 U of SAP enzyme was added to the 10 µl extension product and incubated at 37°C for 1 hour, and then the enzyme was inactivated at 75°C for 15 minutes. The extension product was purified to remove the excess primers and ddNTP.

Capillary electrophoresis sequencing

The purified extension product (0.5 µl) was well mixed with 0.5 µl of Liz120 internal standard (ABI) and 9 µl of formamide. After denaturation at 95°C for 5 minutes, the samples were loaded onto the ABI 3130XL sequencer for sequence analysis. The raw data collected from the ABI 3130XL sequencer were analyzed with GeneMapper 4.1 software (AppliedBiosystems Co., Ltd., USA).

Statistical analysis

All of the experimental data was analyzed using SPSS17.0 software. The measurement data is expressed as mean ± standard deviation (SD). The difference between 2 independent groups was compared using the t test. The compliance of the allele frequency of genome-type distributions of the MCI group and the control group with the Hardy-Weinberg Law of genetic equilibrium was determined using the χ^2 test. The odds ratio (OR) and the 95% confidence interval (95% *CI*) were calculated to

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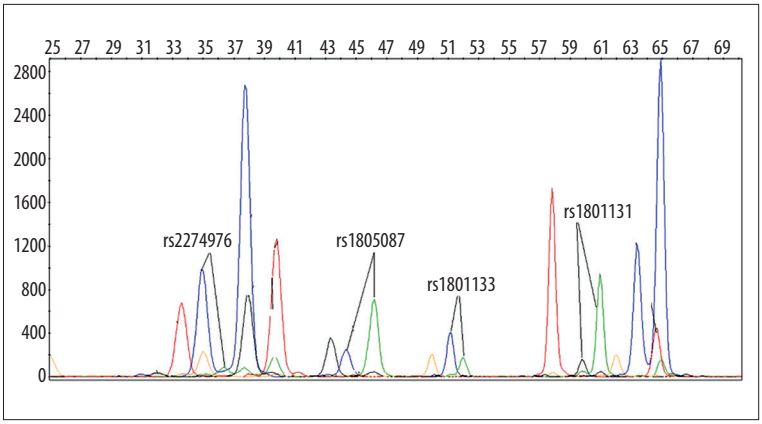

Figure 1. SNaPshot sequencing. (ddGTP – blue peaks; ddATP – green peak; ddTTP – red peak; ddCTP – black peak).

estimate the relative risk of disease from the gene mutation; α=0.05 was used as a significance standard test.

Results

Comparison of the general biochemical indexes of the 2 groups

As shown in Table 1, there was no statistical significant difference in the baseline data, such as age, gender, education (ED), high blood pressure (EH), diabetes type 2 (DM), diastolic blood pressure (DBP), glucose (GLU), total cholesterol (TC), and HDL-C, between the MCI group and the control group (P>0.05). The levels of systolic blood pressure (SBP), triglyceride (TG), LDL-C, and HCY in the patient group were significantly higher than those in the control group (P<0.05).

SNaPshot sequencing

The wild-type AA homozygote of *MTHFR* at the rs1801131 locus (A1298C) showed a single A peak; the mutant CC homozygote showed a single C peak; and the A/C heterozygote showed an AC double-peak. The wild-type CC homozygote at re1801133 locus (C677T) showed a single G peak; the mutant TT homozygote showed a single A peak; and the C/T heterozygote showed an A/G double-peak. The wild-type GG homozygous at the rs2274976 locus (G1968A) showed a single G peak; the mutant AA homozygote showed a single A peak; the G/A heterozygote showed a G/A double-peak. For the MS gene at the rs1805087 locus (A2756G), the wild-type AA homozygote showed a single A peak; the mutant GG homozygote showed a single G peak; and the heterozygote A/G showed an A/G double-peak (Figure 1).

Hardy-Weinberg genetic equilibrium test

The distribution of genotype frequencies of *MTHFR* at rs1801131, rs1801133, and rs2274976 *loci* and MS gene at rs1805087 locus in the MCI group and the control group were calculated using the χ^2 test. The results were consistent with the Hardy-Weinberg equilibrium (P>0.05). At the rs1801131 locus, the MCI group χ^2=0.870, P=0.351; the control group χ^2=2.924, P=0.087; at the rs1801133 locus, the MCI group χ^2=1.143, P 0.285; the control group χ^2=0.689, P=0.407; at the rs2274976 locus, the MCI group χ^2=1.132, P=0.287; the control group χ^2=0.417, P=0.518; at the rs1805087 locus, the MCI group χ^2=1.40, P=0.237; the control group χ^2=0.169, P=0.68. These results indicated that the sample is a good representation of the population.

The comparison of the genotype frequencies of MTHFR and MS and the allele frequency in Xinjiang Uygur

As shown in Table 2, there were significant differences in the genotype frequencies and allele frequencies in the MTHFR rs1801131 locus (A1298C) between the MCI group and the control group (P<0.05). Uighur patients who carried the C allele had a higher risk for MCI (*OR=1.525, 95%CI: 1.038–2.241, P=0.031*). The genotype frequencies and the allele frequencies at the rs1801133 and rs2274976 *loci* in the MCI group and the control group were not statistically different (*P>0.05).* There were differences in the genotype frequencies and the allele frequency of the MS gene at rs1805087 locus (A2756G) in the MCI group and the control group (*P<0.05*). Uighur patients who carried the G alleles had a higher risk for MCI (*OR=1.801, 95%CI: 1.168–2.775, P=0.007*).

Non-conditional Logistic regression analysis for MCI risk factors

A non-conditional logistic regression analysis was used to analyze the data set. In this analysis, MCI was used as a dependent variable and there were a total of 13 independent variables: age, gender, ED, EH, DM, BG, TG, TC, LDL-C, the 3 *MTHFR* polymorphic *loci* (C677T, A1298C, and G1968A), and the polymorphic locus in *MS* (A2756G). As shown in Table 3, ED, TG, LDL-C, and HCY, as well as the A2756G (rs1805087) polymorphism, were independent risk factors for MCI in the Uighur population in

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Table 2. Genotype frequencies and allele frequencies of MTHFR and MS n(%).

Site	Genotype	MCI group		Control group		$\chi 2$	P
rs1801131	AA	61	(0.47)	72	(0.55)	8.179	0.017
	AC	52	(0.4)	55	(0.42)		
	CC	16	(0.13)	4	(0.03)		
	A	174	(0.67)	199	(0.76)	4.645	0.031
	C	84	(0.33)	63	(0.24)		
rs1801133	CC	62	(0.48)	67	(0.51)	3.07	0.214
	CT	51	(0.4)	56	(0.43)		
	TT	16	(0.12)	8	(0.06)		
	C	175	(0.68)	190	(0.72)	1.366	0.24
	T	83	(0.32)	72	(0.28)		
rs2274976	GG	116	(0.9)	115	(0.88)	0.322	0.851
	AG	12	(0.09)	15	(0.11)		
	AA	1	(0.01)	1	(0.01)		
	G	244	(0.95)	245	(0.94)	0.262	0.609
	A	14	(0.05)	17	(0.06)		
rs1805087	AA	74	(0.57)	93	(0.71)	6.695	0.035
	AG	44	(0.34)	34	(0.26)		
	GG	11	(0.09)	4	(0.03)		
	A	192	(0.74)	220	(0.84)	7.206	0.007
	G	66	(0.26)	42	(0.16)		

Table 3. Non-conditional logistic regression analysis of MCI risk factors.

Factors	B	S.E.	χ^2	P	OR	95% CI
ED	0.86	0.328	6.83	0.009	2.357	1.239–4.482
TG	0.67	0.137	24.32	0.000	1.961	1.501–2.563
LDL-C	2.11	0.442	22.79	0.000	8.244	3.467–19.602
Hcy	0.20	0.043	21.57	0.000	1.221	1.121–1.328
rs1805087	0.82	0.322	6.45	0.011	2.265	1.205–4.256

Xinjiang, while polymorphisms C677T, A1298C, and G1968A in *MTHFR* were not. The A>G mutation in the *MS* gene rs1805087 was an independent risk factor for MCI in the Uyghur people. The relative risk of MCI for people who carry the G allele was increased (OR=2.265, 95% CI: 1.205–4.256, P=0.011).

Discussion

Elevated HCY is an independent risk factor for cerebrovascular disease, vascular cognitive impairment, and vascular dementia [3,4]. Ninety percent of the studies on the prospective and cross-section showed that HHCY and decreased vitamin B level lead to cognitive decline [5]. Framingham et al. reported that every 5 μmol/L increase in HCY concentration leads to a 40% increase in the risk of AD [6]. Cognitive impairment caused by HHCY is mainly manifested in the cognitive domain, such as non-text, memorization, visual spatial skills, and information processing, particularly in attention and executive function disorders [7–9]. Further research showed that HHCY affects cognitive functioning though direct DNA damage, excitatory neurotoxicity, and induction of neuron apoptosis.

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MTHFR is a key enzyme in HCY remethylation to methionine, and converts 5,10 -methylenetetrahydrofolate to 5-methyltetrehydofolate. The human *MTHFR* is located on chromosome 1p36.3, has 11 exons, and a CDS length of 2.2 Kbp. Kang et al. [10] first reported the alanine-valine missense mutation at position 677 of *MTHFR*. This mutation reduces the thermotolerance and activity of the enzyme, thereby affecting the HCY remethylation and resulting in a rise in plasma HCY., It also leads to reduced levels of serum folic acid, methionine, and S-adenosyl methionine. In clinical practice, these changes result in developmental delay, mental retardation, abnormal movements, mental problems, cerebral atrophy, demyelination, and thrombosis [11].

Previous studies have identified several single-nucleotide polymorphism (SNP) *loci* in *MTHFR*, of which, C677T, A1298C, and G1968A are closely related to MTHFR activity. However, the effects are different in different populations, geographic regions, and ethnic groups. There are many studies of the relationship between the C677T polymorphism of *MTHFR*, HCY levels, and the resulting cognitive functions. An Australian study on the association between cognitive function and the *MTHFR* C677T polymorphism [12] showed that, in 1778 healthy older men, 46% of the TT genotype carriers had cognitive impairments. A study on a population with cognitive decline in Italy [13] has shown that the HCY level of MCI patients who carried the *MTHFR* 677 TT genotype was higher than the control group with the same genotype, and their HCY levels were higher than the MCI patients who carried the other genotypes (677CT and 677CC). In a recent study of HCY levels in older men and the C677T polymorphism of the *MTHFR* and Alzheimer's disease [14], it was reported that among 4227 elderly men (age 70 to 89) who were monitored for 5.8 years, the risk of developing dementia was 1.48 times higher if the men had an HCY serum level 2 times above normal. Specifically, in males with HCY levels higher than 15 μmol/L, the risk of dementia was 1.36 times higher than in people with normal HCY levels. The risk of dementia was 1.25 times higher in males carrying the TT genotype. Among female patients, it was shown that the 677TT genotype carriers have lower cognitive function [15]. However, some cohort studies have shown that *MTHFR* C677T polymorphism is not associated with cognitive function [16–19]. A meta-analysis on the *MTHFR* C677T polymorphism and AD [20] has shown that the *MTHFR* C677T polymorphism is related to AD in Asians but not in Caucasians. Our study showed that the *MTHFR* C677T SNP was not related to MCI in the Xinjiang Uygur population. Considering that the Uighur people are Caucasian and MCI is a precursor of AD, the decline of cognitive function in AD may be a result of many factors. *MTHFR* C677T SNP may not be an independent risk factor for MCI in the Xinjiang Uygur population.

The *MS* A2756G mutation in a vitamin B6-deficient population can lead to a moderate elevation of serum HCY, and it could be a risk factor for AD [21]. In this study, we found that there were statistically significant differences in the genotype frequency and allele frequency of the *MS* A2756G polymorphism between the MCI group and the control group in the Xinjiang Uygur population ($p<0.05$). Uighur people who carried the G allele had a 1.801 times higher risk of having MCI. After gender grouping, our analysis showed that there were differences in allele frequencies of the *MS* A2756G among the male groups. Uighur males who carried the G allele had a 1.801 times higher risk for MCI, suggesting that the G alleles could be a male MCI susceptibility factor. Further analysis by multifactor non-conditional logistic regression showed that the *MS* (*rs1805087*) A2756G point mutation was an independent risk factor for MCI. Comparing the *MS* A2756G heterozygous and homozygous population with the wild-type population in the Uygur people, the risk of MCI was increased by 2.265 times ($P<0.05$), suggesting a correlation between *MS* A2756G with MCI in the Uygur population and it was significant among Uighur men after gender grouping. The G allele of the *MS* A2756G polymorphism could an indicator for genetic susceptibility of MCI in Uighur men.

Conclusions

Our study showed some results that were not consistent with previous reports in China and abroad, which may be due to differences in inclusion criteria, nationality, geological regions, genetic heterogeneity, environment, and lifestyle of the study populations. Although this study showed that the *MS* A2756G mutation could be an independent risk factor for MCI in the Xinjiang Uygur population, there were only a few cases in this study. Further studies with a larger sample sizes are needed to confirm this result.

References:

1. Feng L, Isaac V, Sim S et al: Associations between elevated homocysteine, cognitive impairment, and reduced white matter volume in healthy old adults. Am J Geriatr Psychiatry, 2013; 21(2): 164–72
2. Al Li-Ke-Mu: Hyperhomocysteinemia and cognitive impairment. Chinese Journal of Arteriosclerosis, 2010; 11: 922–24
3. Yuanyuan Z, Bennu Z: Study on homocysteine in Alzheimer disease and vascular dementia. Journal of Apoplexy and Nervous Diseases, 2007; 10(24): 573–75
4. Xiaojuan W, Juntao L, Weiping P et al: Relationship between Vascular Cognitive Impairment with Serum Homocysteine and Carotid Artherosclerosis. Chinese Journal of Stroke, 2010; 5(6): 438–39
5. Smith AD: The worldwide challenge of the dementias: a role for B-vitamins and homocysteine. Food Nutr Bull, 2008; 29: S143–72
6. Seshasri S, Beiser A, Selhub J et al: Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. New Engl J Med, 2002; 346: 476–83

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7. Troen A, Rosenberg I: Homocysteine and cognitive function. Semin Vasc Med, 2005; 5(2): 209–14
8. Haan MN, Miller JW, Aiello AE et al: Homocysteine,B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on aging. Am J Clin Nutr, 2007; 85(2): 511–17
9. Roffman JL, Weiss AP, Deckersbach T et al: Effects of the methylenetetrahydrofolate reductase(MTHFR)C667T polymorphism on executive function in schizophrenia. Schizophr Res, 2007; 92(1–3): 181–88
10. Kang SS, Wong PW: Genetic and nongenetic factors for moderate hyper homocyst(e)inemia. Atherosclerosis, 1996; 119(2): 135–38
11. Thomas MA, Rosenblatt DS: Severe methylenetetrahydro -folate reductase deficiency. In: Ueland PM, Rozen R (eds.). MTHFR Polymorphism and Disease, Landes Bioscience, 2005; 41–53
12. Ford AH, Flicker L, Hankey GJ et al: Homocysteine, methylenetetrahydrofolate reductase C677T polymorphism and cognitive impairment: the health in men study. Molecular Psychiatry, 2012; 17: 559–66
13. Gaetano G, Francesca U, Claudia A et al: Hyperhomocysteinemia, intima-media thickness and C677T MTHFR gene polymorphism: A correlation study in patients with cognitive impairment. Atherosclerosis, 2009; 206: 309–13
14. Ford AH, Flicker L, Alfonso H et al: Plasma homocysteine and MTHFRC677T polymorphism as risk factors for incident dementia. J Neurol Neurosurg Psychiatry, 2012; 83: 70–75
15. Elkins JS, Johnson SC, Ziv E et al: Methylenetetrahydrofolate reductase C677T polymorphism and cognitive function in older women. Am J of Epidemiol, 2007; 166(6): 672–78
16. Moorthy D, Peter I, Scott TM et al: Status of Vitamins B-12 and B-6 but not of folate, Homocysteine and the Methylenetetrahydrofolate Reductase C677T Polymorphism Are Associated with Impaired Cognition and Depression in Adults. J Nutr, 2012; 142(8): 1554–60
17. Schiepers OJ, van Boxtel MPJ, de Groot RH et al: Genetic variation in folate metabolism is not associated with cognitive functioning or mood in healthy adults. Prog Neuropsychopharmacol Biol Psychiatry, 2011; 35(7): 1682–88
18. Schiepers OJ, van Boxtel MP, Harris SE et al: MTHFR polymorphisms and cognitive ageing in the ninth decade: the Lothian Birth Cohort 1921. Genes Brain Behavior, 2011; 10: 354–64
19. Ferlazzo N, Gorgone G, Caccamo D et al: The 894G > T (Glu298Asp) Variant in the Endothelial NOS Gene and MTHFR Polymorphisms Influence Homocysteine Levels in Patients with Cognitive Decline. Neuromol Med, 2011; 13: 167–74
20. Hua Y, Zhao H, Kong Y et al: Association between the MTHFR gene and Alzheimer's disease: A meta-analysis. Int J Neurosci, 2011; 121: 462–71
21. Beyer K, Lao JI, Latorre P et al: Methionine synthase polymorphism is a risk factor for Alzheimer disease. Neuroreport, 2003; 14: 1391–94

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