Plasma Homocysteine and Gene Polymorphisms Associated with the Risk of Hyperlipidemia in Northern Chinese Subjects[1]

LEI HUANG, XIAO-MING SONG, WEN-LI ZHU, AND YONG LI[2]

Department of Nutrition and Food Hygiene, School of Public Health, Peking University, Beijing 100083, China

Objective To examine the relationship between occurrence of hyperlipidemia, plasma homocysteine and polymorphisms of methylenetetra hydrofolate reductase (MTHFR) gene and methionine synthase (MS) gene. **Methods** A total of 192 hyperlipidemia patients were selected and divided into hypercholesterolemia group, hypertriglyceridemia group, and combined hyperlipidemia group. Another 208 normal individuals were selected as control. Total plasma homocysteine (tHcy) concentration was measured by high-performance liquid chromatography (HPLC). Lipid profiles were measured for all subjects. The polymorphisms of *MTHFR* gene C677T and *MS* gene A2756G were analyzed by PCR-RFLP. **Results** The tHcy concentration in the combined hyperlipidemia patients was significantly higher than that in the control (15.95 μmol/L *vs* 13.43 μmol/L, $P<0.05$). The prevalence of hyperhomocysteinemia (HHcy) in the combined hyperlipidemia group was significantly higher than that in the control (42.2% *vs* 23.0%, $P=0.015$), with the odds ratio (OR) of 3.339 (95%CI: 1.260-8.849). The hyperlipidemia patients with HHcy had a higher concentration of total cholesterol (TC) than that in the normal tHcy patients (5.67±0.95 mmol/L *vs* 5.47±0.92 mmol/L, $P=0.034$). There was no significant difference in genotype or allele frequencies of *MTHFR* C677T between the hyperlipidemic and control groups. The hyperlipidemia patients with *MTHFR* CT/TT genotype had a higher concentration of triglyceride (TG) than those with CC genotype (2.24±1.75 mmol/L *vs* 1.87±0.95 mmol/L, $P<0.05$). Individuals with CT/TT genotype had a higher concentration of tHcy than those with 677CC genotype both in the hyperlipidemia group (12.61±1.24 μmol/L *vs* 11.20±1.37 μmol/L, $P<0.05$) and in the control group (14.04±1.48 μmol/L *vs* 12.61±1.24 μmol/L, $P<0.05$). The percentage of *MS* 2756 GG/AG genotype in the combined hyperlipidemia group was significantly higher than that in the control (26.7% *vs* 13.0%, $P=0.012$), with the OR of 3.121 (95%CI: 1.288-7.651). The hyperlipidemia patients with *MS* 2756AG/GG genotype had a higher concentration of TC (5.87± 0.89 mmol/L *vs* 5.46±0.93 mmol/L, $P<0.05$) and LDL-C (3.29±0.81 mmol/L *vs* 2.94±0.85 mmol/L, $P<0.05$) than those with AA genotype. However, individuals with 2756AG/GG genotype showed no significant difference in tHcy among those with AA genotype. **Conclusion** HHcy and *MS* A2756G mutation may be the risk factors for combined hyperlipidemia. Further study is needed to confirm the role of HHcy and *MS* A2756G mutation in the development of hyperlipidemia.

Key words: Methylenetetra hydrofolate reductase; Methionine synthase; Gene polymorphism; Homocysteine; Hyperlipidemia

REFERENCES

1. Brattstrom L, Wilcken D E, Ohrvik J, *et al.* (1998). Common methylenetetrahydrofolate reductase gene mutation leads to hyperhomocysteinemia but not to vascular disease: the result of a meta-analysis. *Circulation* **98**(23), 2520-2526.
2. McCully K S (1996). Homocysteine and vascular disease. *Nat Med* **2**(4), 386-389.
3. den Heijer M, Rosendaal F R, Blom H J, *et al.* (1998). Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost* **80**(6), 874-877.
4. Ueland P M, Refsum H, Beresford S A, *et al.* (2000). The controversy over homocysteine and cardiovascular risk. *Am J Clin Nutr* **72**(2), 324-332.
5. Boushey C J, Beresford S A, Omenn G S, *et al.* (1995). A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *Jama* **274**(13), 1049-1057.
6. Aguilar B, Rojas J C, Collados M T (2004). Metabolism of homocysteine and its relationship with cardiovascular disease. *J Thromb Thrombolysis* **18**(2), 75-87.
7. Klerk M, Verhoef P, Clarke R, *et al.* (2002). MTHFR 677C-->T polymorphism and risk of coronary heart disease: a meta-analysis. *Jama* **288**(16), 2023-2031.
8. Leclerc D, Campeau E, Goyette P, *et al.* (1996). Human methionine synthase: cDNA cloning and identification of mutations in patients of the cblG complementation group of folate/cobalamin disorders. *Hum Mol Genet* **5**(12), 1867-1874.
9. Xiao Y, Zhang Z T, Wang J B, *et al*. (2003). Effects of dietary intervention on hyperlipidemia in eight communities of Beijing, China. *Biomed Environ Sci* **16**(2), 112-118.
10. te Poele-Pothoff M T, van den Berq M, Franken D G, *et al.* (1995). Three different methods for the determination of total

[1]This study was supported by Beijing Natural Science Foundation, China (No. 7072044).

[2]Correspondence should be addressed to Yong LI. Tel & Fax: 86-10-82801177. E-mail: liyong@bjmu.edu.cn

Biographical note of the first author: Lei HUANG, female, born in 1981, Ph. D. candidate in Department of Nutrition and Food Hygiene, School of Public Health, Peking University, majoring in nutrition and molecular biology.

0895-3988/2008
CN 11-2816/Q

homocysteine in plasma. *Ann Clin Biochem* **32**(Pt 2), 218-220.
11. Skibola C F, Smith M T, Kane E, *et al.* (1999). Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults. *Proc Natl Acad Sci U S A* **96**(22), 12810-12815.
12. Zhu W L, Cheng J, Dao J J, *et al.* (2004). Polymorphism of methionine synthase gene in nuclear families of congenital heart disease. *Biomed Environ Sci* **17**(1), 57-64.
13. Nygard O, Vollset S E, Refsum H, *et al.* (1995). Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. *Jama* **274**(19), 1526-1533.
14. Karmin O, Lynn E G, Chung Y H, *et al.* (1998). Homocysteine stimulates the production and secretion of cholesterol in hepatic cells. *Biochim Biophys Acta* **1393**(2-3), 317-324.
15. Werstuck G H, Lentz S R, Dayal S, *et al.* (2001). Homocysteine-induced endoplasmic reticulum stress causes dysregulation of the cholesterol and triglyceride biosynthetic pathways. *J Clin Invest* **107**(10), 1263-1273.
16. Liao D, Tan H, Hui R, *et al.* (2006). Hyperhomocysteinemia decreases circulating high-density lipoprotein by inhibiting apolipoprotein A-I Protein synthesis and enhancing HDL cholesterol clearance. *Circ Res* **99**(6), 598-606.
17. Li Y, Cheng J, Zhu W L, *et al.* (2005). Study of serum Hcy and polymorphisms of Hcy metabolic enzymes in 192 families affected by congenital heart disease. *Beijing Da Xue Xue Bao* **37**(1), 75-80. (In Chinese)
18. Frosst P, Blom H J, Milos R, *et al.* (1995). A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* **10**(1), 111-113.
19. Yilmaz H, Agachan B, Isbir T, *et al.* (2003). Is there additional effect of MTHFR C677T mutation on lipid abnormalities in renal allograft recipients? *Transplant Proc* **35**(4), 1390-1392.
20. Zuntar I, Antoljak N, Vrkic N, *et al.* (2006). Association of methylenetetrahydrofolate (MTHFR) and apolipoprotein E (apo E) genotypes with homocysteine, vitamin and lipid levels in carotid stenosis. *Coll Antropol* **30**(4), 871-878.
21. Veerkamp M J, de Graaf J, den Heijer M, *et al.* (2003). Plasma homocysteine in subjects with familial combined hyperlipidemia. *Atherosclerosis* **166**(1), 111-117.
22. Zhang G S, Dai C W (2001). Gene polymorphisms of homocysteine metabolism related enzymes in Chinese patients with occlusive coronary artery or cerebral vascular diseases. *Thrombosis Research* **104** (3), 189-195.
23. Laraqui A, Allami A, Carrie A, *et al.* (2006). Influence of methionine synthase (A2756G) and methionine synthase reductase (A66G) polymorphisms on plasma homocysteine levels and relation to risk of coronary artery disease. *Acta Cardiol* **61**(1), 51-61.
24. Harmon D L, Shields D C, Woodside J V, *et al.* (1999). Methionine synthase D919G polymorphism is a significant but modest determinant of circulating homocysteine concentrations. *Genet Epidemiol* **17**(4), 298-309.
25. Jacques P F, Bostom A G, Selhub J, *et al.* (2003). Effects of polymorphisms of methionine synthase and methionine synthase reductase on total plasma homocysteine in the NHLBI Family Heart Study. *Atherosclerosis* **166**(1), 49-55.
26. Hyndman M E, Bridge P J, Warnica J W, *et al.* (2000). Effect of heterozygosity for the methionine synthase 2756 A > G mutationon the risk for recurrent cardiovascular events. *Am J Cardiol* **86**(10), 1144-1146, A9.
27. Morita H, Kurihara H, Sugiyama T, *et al.* (1999). Polymorphism of the methionine synthase gene-association with homocysteine metabolism and late-onset vascular diseasesin the Japanese population. *Arteriol Thromb Vasc Biol* **19**(2), 298-302.
28. Rafique S, Guardascione M, Osman E, *et al*. (1992). Reversal of extrahepatic membrane cholesterol deposition in patients with chronic liver diseases by S-adenosyl-L-methionine. *Clin Sci (Lond)* **83**(3), 353-356.
29. Chawla R K, Bonkovsky H L, Galambos J T (1990). Biochemistry and pharmacology of S-adenosyl-L-methionine and rationale for its use in liver disease. *Drugs* **40**(Suppl 3), 98-110.
30. Klerk M, Lievers K J, Kluijtmans L A, *et al*. (2003). The 2756A>G variant in the gene encoding methionine synthase: its relation with plasma homocysteine levels and risk of coronary heartdisease in a Dutch case-control study. *Thromb Res* **110**(2-3), 87-91.

(*Received February* 1, 2008 *Accepted July* 17, 2008)