Letter to the Editor

Multi-Genetic Origins of Phenotypic Markers of the Risk of Cardiovascular Disease

Orkut Guclu, Celal Yavuz, Oguz Karahan

Medical School of Dicle University, Department of Cardiovascular Surgery, Diyarbakir, Turkey

Key words: **MTHFR gene, polymorphism, homocysteine, phenotypic reflections, cardiovascular disease, risk factor.**

Manuscript received: June 8, 2012;
Accepted: November 26, 2012.

Address:
Oguz Karahan

Medical School
Dicle University
Department of
Cardiovascular Surgery
Diyarbakir, Turkey
e-mail:
oguzk2002@gmail.com

We read with great interest the article by Eftychiou et al in reference to their instituting measurements of homocysteine levels and MTHFR polymorphisms in young patients with acute myocardial infarction.[1] We thank them for their important contribution to clarifying populational genetic mapping and congenital cardiovascular reflections.

Homocysteine is a substance of whole blood that is made when the amino acid methionine is broken down in the body.[2] Elevated homocysteine levels have been suggested as a risk factor for atherosclerosis and cardiovascular disease.[2] There have been some genetic regulatory mechanisms described in the literature. The methylenetetrahydrofolate reductase (MTHFR) gene is the main regulator gene of this mechanism. In carrying the T allele instead of the A allele at MTHFR C677T gene position 677, the enzyme is more thermolabile and has lower activity.[3] This gene deletion leads to degradation in the proportion of serum folic acid levels and a rise in the homocysteine concentration.[2,3]

Several authors have described a pathogenetic relationship between prothrombotic gene mutations and vascular disorders. While some of these reports referred to familial cardiovascular events, most of the studies focused on population screening for such disorders. For example, MTHFR gene mutations were reported by Yucel et al in a family with premature cardiovascular disease.[3] However, this study included the investigation of other actual single deletions. Additionally, genotypic changes did not affect the phenotypic markers, such as two family members with the MTHFR homozygote mutation.[3] Aslan et al claimed that MTHFR A1298C gene mutation can increase thrombotic events in lung cancer patients with deep venous thrombosis. Despite the phenotypic reflections not being declared, this report presented the collaborative efficacy of common multiple single gene deletions.[4] In a report by Ozen et al, MTHFR gene deletion was blamed for an important risk factor in patients with *thromboangiitis obliterans*.[5] However, the phenotype was neglected in this study. An ethnicity study was carried out on the Pomeranian population of Espirito Santo, Brazil, by Stur et al.[6] This study claimed that there was a gene flow between the general and isolated populations; however, it ignored the phenotypical variations of this gene flow (for example, homocysteine levels were not examined).

The definition of phenotypes has had a key role in clarifying genetics.[7] The genetic variations should be investigated along with their phenotypic reflections. Thus, we congratulate Eftychiou et al for illuminating the MTHFR gene variants with reflections on cardiogenesis. We suggest, however, that genetic interactions be evaluated together for the exact determination of phenotypic biomarker effects. This report would be better if presented with the addition of homocysteine and folic acid levels.

References

1. Eftychiou C, Antoniades L, Makri L, et al. Homocysteine levels and MTHFR polymorphisms in young patients with acute myocardial infarction: a case control study. Hellenic J Cardiol. 2012; 53: 189-194.
2. Varga EA, Sturm AC, Misita CP, Moll S. Cardiology patient pages. Homocysteine and MTHFR mutations: relation to thrombosis and coronary artery disease. Circulation. 2005; 111: e289-293.
3. Yucel O, Karahan O, Zorlu A, Manduz S. Familial genetic risk factors in premature cardiovascular disease: a family study. Mol Biol Rep. 2012; 39: 6141-6147.
4. Arslan S, Manduz S, Epöztürk K, Karahan O, Akkurt I. Association of deep venous thrombosis with prothrombotic gene polymorphism identified in lung cancer cases. Mol Biol Rep. 2011; 38: 2395-2400.
5. Ozen, F, Manduz S Katrancıogu N, Karahan O, Koksal B, Ozdemir O. Role of prothrombotic gene polymorphism in patients with thromboangiitis obliterans. Turkiye Klinikleri J Cardiovasc Sci. 2009; 21: 160-164.
6. Stur E, Silveira AN, Selvatici LS, et al. Polymorphism analysis of MTHFR, factor II, and factor V genes in the Pomeranian population of Espirito Santo, Brazil. Genet Test Mol Biomarkers. 2012; 16: 219-222.
7. Tohsato Y, Mori H. Phenotype profiling of single gene deletion mutants of E. coli using Biolog technology. Genome Inform. 2008; 21: 42-52.

The author replies

First I would like to thank the authors of the letter for their interest shown in our work and congratulate them on their useful remarks concerning homocysteine metabolism and genetics.

The relationship between homocysteine levels and coronary artery disease (CAD) has already been established, while hyperhomocysteinemia is also considered to be a risk factor for the presence of premature CAD. Whether this relationship is causative or not is still under debate in the literature. Also well known is the existence of the reverse relationship between homocysteine levels and folic acid, due to the crucial role of folate in methionine metabolism. However low levels of folic acid are not really a strong phenotype that is necessarily associated with homocysteine levels. We are all familiar with the disappointing results of the NORVIT and HOPE-2 studies, which also cast doubt upon the direct role of homocysteine in CAD and the idea of intervening in its levels. In these studies, and many others as well, folic acid was given to patients and homocysteine levels dropped significantly, but the risk of CAD remained as high as when no folic acid was given.[1-6]

On the other hand, not much has been published on the reverse relationship between the levels of homocysteine and HDL, where a likely possible mechanism of a causative relationship between homocysteine and CAD through low HDL levels is shown.[7-9] This is a very important issue, which was well examined in our study, and probably merits further investigation.

I believe that when we encounter high homocysteine levels, especially in young patients, instead of giving folic acid (which is not recommended anyway for primary or secondary prevention), we should be looking for ways to raise the HDL levels as well as strictly controlling all other risk factors. In any case, raising the HDL levels is not an easy task and a lot of research work remains to be done.

Dr Christos Eftychiou MD, PhD, FESC
Interventional Cardiologist
Cardiology Department, Nicosia General Hospital, Cyprus
email: chiou6christos@yahoo.com

References

1. Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease, and drug therapy. J Lab Clin Med. 1989; 114: 473-501.
2. Christen WG, Ajani UA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease: causal or casual? Arch Intern Med. 2000; 160: 422-434.
3. Stein JH, McBride PE. Hyperhomocysteinemia and atherosclerotic vascular disease: pathophysiology, screening, and treatment. off. Arch Intern Med. 1998; 158: 1301-1306.
4. Sadeghian S, Fallahi F, Salarifar M, et al. Homocysteine, vitamin B12 and folate levels in premature coronary artery disease. BMC Cardiovasc Disord. 2006; 6: 38.
5. Bønaa KH, Njølstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med. 2006; 354: 1578-1588.
6. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006; 354: 1567-1577.
7. Eftychiou C, Antoniades L, Makri L, et al. Homocysteine levels and MTHFR polymorphisms in young patients with acute myocardial infarction: a case control study. Hellenic J Cardiol. 2012; 53: 189-194.
8. Liao D, Tan H, Hui R, et al. Hyperhomocysteinemia decreases circulating high-density lipoprotein by inhibiting apolipoprotein A-I Protein synthesis and enhancing HDL cholesterol clearance. Circ Res. 2006; 99: 598-606.
9. Mikael LG, Genest J Jr, Rozen R. Elevated homocysteine reduces apolipoprotein A-I expression in hyperhomocysteinemic mice and in males with coronary artery disease. Circ Res. 2006; 98: 564-571.