Abstract

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Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease.

Kluijtmans LA, van den Heuvel LP, Boers GH, Frosst P, Stevens EM, van Oost BA, den Heijer M, Trijbels FJ, Rozen R, Blom HJ.

Department of Pediatrics, University Hospital Nijmegen, The Netherlands.

BACKGROUND AND OBJECTIVES: Mild hyperhomocysteinemia is an established risk factor for cardiovascular disease. Genetic aberrations in the cystathionine beta-synthase (CBS) and methylenetetrahydrofolate reductase (MTHFR) genes may account for reduced enzyme activities and elevated plasma homocysteine levels. In 15 unrelated Dutch patients with homozygous CBS deficiency, we observed the 833T-->C (I278T) mutation in 50% of the alleles. Very recently, we identified a common mutation (677C-->T; A-->V) in the MTHFR gene, which, in homozygous state, is responsible for the thermolabile phenotype and which is associated with decreased specific MTHRF activity and elevated homocysteine levels.

METHODS: We screened 60 cardiovascular patients and 111 controls for these two mutations, to determine whether these mutations are risk factors for premature cardiovascular disease.

RESULTS: Heterozygosity for the 833T-->C mutation in the CBS gene was observed in one individual of the control group but was absent in patients with premature cardiovascular disease. Homozygosity for the 677C-->T mutation in the MTHFR gene was found in (15%) of 60 cardiovascular patients and in only 6 (approximately 5%) of 111 control individuals (odds ratio 3.1 [95% confidence interval 1.0-9.2]).

CONCLUSION: Because of both the high prevalence of the 833T-->C mutation among homozygotes for CBS deficiency and its absence in 60 cardiovascular patients, we may conclude that heterozygosity for CBS deficiency does not appear to be involved in premature cardiovascular disease. However, a frequent homozygous mutation in the MTHFR gene is associated with a threefold increase in risk for premature cardiovascular disease.

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