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MTHFR gene polymorphism, homocysteine and cardiovascular disease.

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Source

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Abstract

Homocysteine is an emerging new risk factor for cardiovascular disease. It is a thiol compound derived from methionine and involved in two main metabolic pathways: the cycle of activated methyl groups, requiring folate and vitamin B12 as cofactors, and the transsulfuration pathway to cystathionine and cysteine requiring vitamin B6 as cofactor. The homocysteine metabolism represents an interesting model of gene-environment interaction. Elevations in homocysteine may be caused by genetic defects in enzymes involved in its metabolism or by deficiencies in cofactor levels. A common polymorphism in the gene coding for the 5,10-methylene tetrahydrofolate reductase (MTHFR) (C677T, Ala --> Val) is associated with a decreased activity of the enzyme due to thermolability. In case of homozygosity for the Val allele, a relative deficiency in the remethylation process of homocysteine into methionine leads to a mild-to-moderate hyperhomocysteinemia, a condition recognized as an independent risk factor for atherosclerosis. The genetic influence of the MTHFR polymorphism on homocysteine levels is attenuated in females in premenopausal age and is not significant in subjects who exhibit serum levels of folate and/or vitamin B12 above the 50th percentile of distribution in the general population. The prevalence of the Val/Val genotype varies among different ethnic groups. It is very low in African populations, whereas in Europe and North America it ranges between 5% and 15%. In Italy an even higher prevalence has been reported in some regions. The question whether the MTHFR polymorphism might be per se an independent contributor to cardiovascular risk is debated. The interaction between this or other genetic factors and environmental/nutritional conditions (i.e. intake of vitamins such as folate) is a key determinant for homocysteine concentrations in healthy conditions as well as in some disease (i.e. in renal disorders). Another example of gene/environment interaction in the field of atherosclerosis is given by the apolipoprotein E polymorphism and its influence in response to diet. The presence of a high prevalence of risk-related allelic variants of such candidate genes within a certain population could serve to locally reinforce the recommendations concerning nutrient intake.

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