Polymorphisms in serine hydroxymethyltransferase 1 and methylenetetrahydrofolate reductase interact to increase cardiovascular disease risk in humans.


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BACKGROUND: The enzymes serine hydroxymethyltransferase 1 (gene name SHMT1) and methylenetetrahydrofolate reductase (gene name MTHFR) regulate key reactions in folate-mediated one-carbon metabolism. Common genetic variants with the potential to influence disease risk exist in both genes.

OBJECTIVE: A prior report from the Normative Aging Study indicated no association of the SHMT1 rs1979277 SNP with cardiovascular disease (CVD), but a strong gene-gene interaction was detected with MTHFR rs1801133.

METHODS: We investigated the effect of the SHMT1 rs1979277 SNP and the SHMT1 rs1979277-MTHFR rs1801133 interaction in 2 epidemiologic cohort studies.

RESULTS: In the Nurses' Health Study (NHS), the MTHFR rs1801133 variant genotypes were associated with an increased CVD risk and there was an interaction between SHMT1 and MTHFR such that the association of the MTHFR rs1801133 CT genotype (vs. CC; the TT genotype could not be evaluated) was stronger in the presence of the SHMT1 rs1979277 TT genotype (OR = 4.34, 95% CI = 1.2, 16.2; P = 0.049). In the Health Professionals Follow-Up Study, the MTHFR rs1801133 genotype was not associated with CVD risk, nor was there an interaction with SHMT1 rs1979277.

CONCLUSIONS: The association of genetic variation in the SHMT1 gene, alone and in interaction with MTHFR, in relation to CVD risk is relatively understudied at the population level and results in the NHS confirmed a past report of gene-gene interaction, which is consistent with mechanisms suggested by basic science studies.

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