

Abstract

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Genetic polymorphisms in homocysteine metabolism and response to folate intake: a comprehensive strategy to elucidate useful genetic information.

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BACKGROUND: Homocysteine is a risk factor for atherosclerosis, and the level of homocysteine in plasma is known to be strongly influenced by genetic factors-not only rare variants, but also common polymorphisms.

OBJECTIVE: This report describes a comprehensive postgenomic strategy for elucidating useful genetic information about homocysteine metabolism.

METHODS: The standard method for gathering such information is the candidate gene approach, which is an effective method based on known biological information. After collecting evidence from independent research projects, a critical epidemiological review permits a determination as to whether a putative association is true or not. A **genome-wide association study (GWAS)**, which requires no biological information, can identify new candidates and confirm associations suggested by the candidate gene approach.

RESULTS: The importance of methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, which was shown in a randomized controlled trial conducted by the present author, and in other studies, was independently confirmed by a large-scale GWAS. GWASs have also identified new candidate genes, but these must be confirmed by independent studies.

CONCLUSION: In homocysteine metabolism, the classical candidate gene approach was sufficiently robust to detect the true association. However, candidate markers newly discovered by GWAS need to be confirmed by well-designed epidemiological studies to determine their significance. International statements, such as CONSORT and STREGA, provide useful principles for conducting such research.

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