

Abstract

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Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults.

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BACKGROUND: Reduction of 5,10-methylenetetrahydrofolate (methyleneTHF), a donor for methylating dUMP to dTMP in DNA synthesis, to 5-methyltetrahydrofolate (methylTHF), the primary methyl donor for methionine synthesis, is catalyzed by 5,10-methylenetetrahydrofolate reductase (MTHFR). A common 677 C --> T polymorphism in the MTHFR gene results in thermolability and reduced MTHFR activity that decreases the pool of methylTHF and increases the pool of methyleneTHF. Recently, another polymorphism in MTHFR (1298 A --> C) has been identified that also results in diminished enzyme activity.

OBJECTIVE AND METHODS: We tested whether carriers of these variant alleles are protected from adult acute leukemia. We analyzed DNA from a case-control study in the United Kingdom of 308 adult acute leukemia patients and 491 age- and sex-matched controls. MTHFR variant alleles were determined by a PCR-restriction fragment length polymorphism assay.

RESULTS: The MTHFR 677TT genotype was lower among 71 acute lymphocytic leukemia (ALL) cases compared with 114 controls, conferring a 4.3-fold decrease in risk of ALL [odds ratio (OR) = 0.23; 95% CI = 0.06-0.81]. We observed a 3-fold reduction in risk of ALL in individuals with the MTHFR 1298AC polymorphism (OR = 0.33; 95% CI = 0.15-0.73) and a 14-fold decreased risk of ALL in those with the MTHFR 1298CC variant allele (OR = 0.07; 95% CI = 0.00-1.77). In acute myeloid leukemia, no significant difference in MTHFR 677 and 1298 genotype frequencies was observed between 237 cases and 377 controls.

CONCLUSIONS: Individuals with the MTHFR 677TT, 1298AC, and 1298CC genotypes have a decreased risk of adult ALL, but not acute myeloid leukemia, which suggests that folate inadequacy may play a key role in the development of ALL.

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