

# Abstract

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## **Polymorphisms in the methylenetetrahydrofolate reductase gene were associated with both the efficacy and the toxicity of methotrexate used for the treatment of rheumatoid arthritis, as evidenced by single locus and haplotype analyses.**

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**OBJECTIVE:** 5,10-Methylenetetrahydrofolate reductase (MTHFR), a key enzyme involved in folate metabolism, has two common polymorphisms that affect enzyme activity. The objective of this study was to examine whether there was a correlation between the genotype or haplotype of the MTHFR gene and the efficacy or toxicity of **methotrexate (MTX)** in the treatment of rheumatoid arthritis.

**METHODS:** MTX-treated rheumatoid arthritis patients (n = 106) were selected from outpatient clinics and used for a retrospective study to examine the correlation between genotypes or haplotypes concerning polymorphisms of the MTHFR gene, and the efficacy or toxicity of MTX. Estimation of the haplotype frequencies was performed by maximum likelihood estimation based on expectation maximization algorithm.

**RESULTS:** Single locus analysis examining each locus separately showed that patients with 1298C were receiving significantly lower doses of MTX compared to patients without [P < 0.05, relative risk (RR) = 2.18, 95% confidence interval (CI) 1.17-4.06], while a higher rate of overall MTX toxicity was observed in patients with 677T than those without (P < 0.05, RR = 1.25, 95% CI 1.05-1.49). An estimation of haplotype frequencies showed that there was no 677T-1298C haplotype in the population. Posterior distribution of the diplotype configuration for each individual was concentrated on a single configuration. Patients with the 677C-1298C haplotype were receiving lower doses of MTX than those without (P < 0.05, RR = 2.14, 95% CI 1.13-4.07), while **subjects with 677T-1298A had a higher frequency of side-effects from MTX** (P < 0.05, RR = 1.42, 95% CI 1.11-1.82).

**CONCLUSIONS:** **Both single locus and haplotype analyses suggest that polymorphisms within the MTHFR gene are associated with both the efficacy and toxicity of MTX in rheumatoid arthritis patients.** Pharmacokinetic studies are necessary to prove the association.

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