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Published by mbeasley on Mon, 09/08/2014 - 2:49pm

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Published on UAB School of Public Health (http://www.soph.uab.edu)

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Racial or ethnic differences in allele frequencies of single-nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene and their influence on response to methotrexate in rheumatoid arthritis.

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Journal
Ann Rheum Dis

Volume
65

Issue
9

Pagination
1213-8

Date Published
2006 Sep

ISSN
0003-4967

Keywords
African Americans, Antirheumatic Agents, Arthritis, Rheumatoid, European Continental Ancestry Group, Gene Frequency, Haplotypes, Humans, Methotrexate, Methylenetetrahydrofolate Reductase (NADPH2), Polymorphism, Single Nucleotide, Prospective Studies, Treatment Outcome

Abstract
BACKGROUND: The anti-folate drug methotrexate (MTX) is commonly used to treat rheumatoid arthritis.

OBJECTIVE: To determine the allele frequencies of five common coding single-nucleotide polymorphisms (SNPs) in the methylenetetrahydrofolate reductase (MTHFR) gene in African-Americans and Caucasians with rheumatoid arthritis and controls to assess whether there are differences in allele frequencies among these ethnic or racial groups and whether these SNPs differentially affect the efficacy or toxicity of MTX.

METHODS: Allele frequencies in the 677, 1298 and 3 additional SNPs in the MTHFR coding region in 223 (193 Caucasians and 30 African-Americans) patients with rheumatoid arthritis who previously participated in one of two prospective clinical trials were characterised, and genotypes were correlated with the efficacy and toxicity of MTX. Another 308 subjects with rheumatoid arthritis who participated in observational studies, one group predominantly Caucasian and the other African-American, as
well as 103 normal controls (53 African-Americans and 50 Caucasians) were used to characterise allele frequencies of these SNPs and their associated haplotypes.

RESULTS: Significantly different allele frequencies were seen in three of the five SNPs and haplotype frequencies between Caucasians and African-Americans. Allele frequencies were similar between patients with rheumatoid arthritis and controls of the same racial or ethnic group. Frequencies of the rs4846051C, 677T and 1298C alleles were 0.33, 0.11 and 0.13, respectively, among African-Americans with rheumatoid arthritis. Among Caucasians with rheumatoid arthritis, these allele frequencies were 0.08 (p<0.001 compared with African-Americans with rheumatoid arthritis), 0.30 (p = 0.002) and 0.34 (p<0.001), respectively. There was no association between SNP alleles or haplotypes and response to MTX as measured by the mean change in the 28-joint Disease Activity Score from baseline values. In Caucasians, the 1298 A (major) allele was associated with a significant increase in MTX-related adverse events characteristic of a recessive genetic effect (odds ratio 15.86, 95% confidence interval 1.51 to 167.01; p = 0.021), confirming previous reports. There was an association between scores of MTX toxicity and the rs4846051 C allele, and haplotypes containing this allele, in African-Americans, but not in Caucasians.

CONCLUSIONS: These results, although preliminary, highlight racial or ethnic differences in frequencies of common MTHFR SNPs. The MTHFR 1298 A and the rs4846051 C alleles were associated with MTX-related adverse events in Caucasians and African-Americans, respectively, but these findings should be replicated in larger studies. The rs4846051 SNP, which is far more common in African-Americans than in Caucasians, can also be proved to be a useful ancestry informative marker in future studies on genetic admixture.

DOI
10.1136/ard.2005.046797
Alternate Journal
PubMed ID
16439441
PubMed Central ID
PMC1798268
Grant List
K23 AR052051 / AR / NIAMS NIH HHS / United States
P60 AR 48095 / AR / NIAMS NIH HHS / United States
P60 AR048095 / AR / NIAMS NIH HHS / United States
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