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Polymorphisms in Folate-Related Enzyme Genes in Idiopathic Infertile Brazilian Men

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Abstract

The aim of the study was to analyze the distribution of the methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase reductase (*MTRR*), and methionine synthase (*MTR*) polymorphisms in idiopathic infertile Brazilian men and fertile men. Case–control study comprising 133 idiopathic infertile Brazilian men with nonobstructive azoospermia ([NOA] n = 55) or severe oligozoospermia ([SO] n = 78) and 173 fertile men as controls. *MTHFR* C677T, A1298C, and G1793A; *MTRR* A66G; and *MTR* A2756G polymorphisms were studied by quantitative polymerase chain reaction (qPCR). The results were analyzed statistically and a *P* value <.05 was considered significant. Single-marker analysis revealed a significant association among *MTHFR* C677T polymorphism and both NOA group ($P = .018$) and SO group ($P < .001$). Considering the *MTHFR* A1298C, *MTHFR* G1793A, and *MTRR* A66G polymorphisms, no difference was found between NOA group and SO group. Regarding the *MTR* A2756G polymorphism, a significant difference was found between NOA and controls, $P = .017$. However, statistical analysis revealed no association between SO group and controls. Combined genotypes of 3 *MTHFR* polymorphisms did not identify a haplotype associated with idiopathic infertility. The combinatory analysis of the 3 polymorphisms *MTHFR*, *MTRR*, and *MTR* did not show difference between cases and controls. The findings suggest the *MTHFR* C677T and *MTR* A2756G polymorphisms could be an important genetic factor predisposing to idiopathic infertility in Brazilian men.

Keywords

male infertility, folate, homocysteine, *MTHFR* gene, *MTRR* gene, *MTR* gene

Introduction

Infertility is a very common health problem that affects approximately 15% to 20% of couples who attempt pregnancy.[1] In almost 50% of infertile couples, the problem is related to the male and in about 15% of these cases genetic abnormalities could be present, including chromosomal aberrations and single-gene mutations.[1,2]

Folate participates in amino acid metabolism, purine and pyrimidine synthesis, and methylation of nucleic acids, proteins, and lipids. Dietary or genetically determined folate deficiency may impair the function of these metabolic pathways and lead to homocysteine (Hcy) accumulation.[3] Homocysteine, a thiol-containing amino acid, originates from the 1-carbon-donating metabolism of methionine and is remethylated to methionine, with folate acting as methyl donors.[4]

Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme involved in folate metabolism. Methionine, the precursor for the universal methyl donor (*S*-adenosylmethionine) is produced through the irreversible transfer of a methyl group from 5-methyltetrahydrofolate. This reaction is regulated by 2 enzymes, methionine synthase (MTR) and methionine synthase reductase (MTRR).[5] Disturbances in the catalytic activity of MTRR could lead to higher levels of Hcy. MTHFR, MTR, and MTRR play an important role in folate metabolism, and Hcy levels could affect DNA synthesis and methylation, leading to an increased oxidative stress[6] and disturbed methylation reactions.[7] Such processes are involved in male infertility.[8,9]

The *MTHFR* gene, located on the short arm of chromosome 1 (1p36.3), presents 3 common polymorphisms involving nucleotides C677T, A1298C, and G1793A. The change of C for T at position 677 causes the substitution of alanine for valine in the MTHFR protein and the consequent reduction

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