Common Polymorphism's Analysis of Thiopurine S-Methyltransferase (TPMT) in Iranian Population

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Abstract

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Objective: Thiopurine S-methyltransferase (TPMT) catalyses the S-methylation of thiopurine drugs. Low activity phenotypes are correlated with several mutations in the TPMT gene and adverse drug reactions. The molecular basis for dissimilar enzymatic activity of TPMT has been established in Caucasians, African-Americans and Southwest Asians, but it remains to be elucidated in Iranian population. Until present, no study on Iranian population has been performed on the known alleles of TPMT. The aim of this study was to investigate the frequencies of four of the most common variants of this gene.

Materials and Methods: This study was conducted during 2007 at the Department of Hematology, Tarbiat Modares University, Tehran, Iran. Using PCR-RFLP and allele specific PCR techniques, allelic variants of the TPMT gene TPMT*2(G238C), TPMT*3B (G460A), TPMT*3C (A719G) and TPMT*3A (G460A and A719G) were genotyped in a normal population of 127 Iranians.

Results: In this study TPMT*2 showed a prevalence of 7.08%. TPMT*3C and *3A were found in 2.47% and 2.18% of the samples, respectively. TPMT*3B variant was not detected in Iranian subjects. 112 out of 127 participants showed homozygote wild type allele.

Conclusion: This study is the first to analyze TPMT allele frequencies in a sample of Iranian population and indicates that TPMT*2 is the most common allele (7.08%) in this population. These results can help to organize national pretreatment strategies in patients with acute lymphoblastic leukemia (ALL) or other diseases requiring thiopurine medication in their standard therapy.

Keywords: Thiopurine S-methyltransferase, Polymorphism Genetic, Pharmaco Genetics

Introduction

Drug metabolizing enzymes participate in the neutralization of xenobiotics and biotransformation of these drugs. Polymorphisms in genes coding drug-metabolizing enzymes can alter the activity of the enzymes for their substrates (1). The anti-cancer prodrugs, 6-mercaptopurine (6-MP) and azathioprine (AZA), are metabolized by thiopurine S-methyltransferase (TPMT) and widely used to treat several diseases such as childhood Acute Lymphoblastic Leukemia (ALL), autoimmune hepatitis, myasthenia gravis and rheumatoid arthritis (2, 3). Thiopurine S-methyltransferase (TPMT, MIM# 187680) is a cytosolic enzyme that catalyzes the S-methylation of aromatic and heterocyclic sulfhydryl compounds like 6-Mercaptopurine (6MP) (4). The TPMT gene is localized on chromosome 6p22.3 and consists of 10 exons. TPMT hypoactivity is inherited as an autosomal co-dominant trait that occurs in 1/300 of general population, also it appears as homozygosity in some polymorphisms causing complete enzyme inactivity. About 10% of individuals have intermediate activity because of heterozygosity (5, 6). Some polymorphisms of TPMT have been shown to interfere with normal optimum activity of this enzyme and cause AZA and 6-MP toxicity. To avoid hematotoxicity associated with TPMT-deficiency, phenotyping and genotyping tests should precede along with thiopurine therapy. TPMT molecular pharmacogenetic studies resulted in the discovery of a series of variant alleles (containing single nucleotide polymorphisms; SNPs) associated with significantly decreased levels of TPMT activity (3). High TPMT activity, results in a greater production of inactive methylated metabolites, which reduces therapeutic efficacy. Con-