



Genetic Analysis of Thiopurine Methyltransferase Polymorphism in Jordanian Population

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Introduction

Thiopurine methyltransferase (TPMT) catalyses the *S*-methylation of thiopurine drugs such as 6-mercaptopurine, 6-thioguanine, and azathiopurine. These drugs have a well-established role as immunosuppressive agents in a variety of chronic inflammatory conditions, haematological neoplasia and in transplant rejection. *TPMT* polymorphisms are the major determinants of interindividual differences in the severe toxicity or efficacy of 6-mercaptopurine. The frequencies of four (*TPMT*2*, *TPMT*3A*, *TPMT*3B* and *TPMT*3C*) variants were investigated in the Jordanian population. The differences in *TPMT* activity results from single nucleotide polymorphisms (SNPs). The wild-type allele is designated as *TPMT*1* and to date, at least 23 variant alleles of *TPMT* gene have been identified. Four alleles (*TPMT*2*, **3A*, **3B* and **3C*) account for 80-95% of inherited *TPMT* deficiency and low enzyme activity.

Several studies have investigated the prevalence of these mutations in different populations. From the four mutations mentioned earlier, the most rare mutation is the *TPMT*3B*. The most frequent allele mutation in Caucasians is *TPMT*3A* while the *TPMT*3C* is the most prevalent allele mutations in African and Asian populations.

Materials and Methods

Blood samples have been collected on Whatman FTA cards from 169 healthy unrelated male volunteers. The study was approved by the ethics committee and all subjects consented, in writing, to the study after full explanation of what was involved. DNA was extracted from the cards. Single nucleotide polymorphisms (SNPs) were genotyped using the Sequenom® MassARRAY technology (Sequenom®, San Diego). DNA samples were studied for the presence of the variants corresponding to the *TPMT*2*, *TPMT*3A*, *TPMT*3B* and *TPMT*3C* alleles.

Results

Two individuals with *TPMT*3A* heterozygote and one individual with *TPMT*3C* heterozygote were the only mutant alleles found in 169 Jordanian subjects. None of the subjects studied had *TPMT*2* or *TPMT*3B* genotypes. Overall, mutant *TPMT* alleles were found in 1.8% of the studied subjects, 166 individuals (98.2%) were apparently homozygous for the wild type (*TPMT*1/*1*).

| Alleles | Gene variants | No. of alleles | % Frequency |
|----------------------|-----------------------|----------------|-------------|
| Total no. of alleles | | 338 | |
| <i>TPMT*1</i> | Wild-type | 335 | 99.11 |
| <i>TPMT*2</i> | c.248G>C | 0 | 0 |
| <i>TPMT*3A</i> | c.460G>A, c.719A>G | 2 | 0.59 |
| <i>TPMT*3B</i> | c.460G>A | 0 | 0 |
| <i>TPMT*3C</i> | c.719A>G | 1 | 0.3 |
| Total mutant alleles | | 3 | 0.89 |

The allelic frequencies of *TPMT* gene in Jordanian population.

Discussion

In the 169 individuals that participated in this study, the only mutant alleles that have been detected were *TPMT*3C* (0.3%) and *TPMT*3A* (0.59%). The frequency of *TPMT*3C* in Jordanian population was similar to the Caucasian populations studied (0.2-1%) [1, 2]. On the other hand, it was lower than those from African descendents [1]. In the case of *TPMT*3A* allele frequency it was much lower than the Caucasian populations studied [1, 2] but similar to the Latin American descendents, African descendents and Middle Eastern descendents (Turkish population [3]). None of the participants from Jordanian population had the *TPMT*2* or *TPMT*3B* mutant alleles. *TPMT*2* have been detected at low frequencies in different populations whereas the *TPMT*3B* is a rare mutation in the different populations studied.

The total percentage frequency of mutant *TPMT* alleles in the Jordanian population (1.8%) is lower than that reported for several populations; e.g. British 10.1% and Ghanaians 14.8% [1], but compatible with that reported for Middle Eastern descendents; e.g. Turkish (2.7%) [3].

Jordanians are Caucasians in their origin but they are considered heterogeneous, this reflects ancient and recent admixture with neighboring populations, and important migratory trends throughout history.

Conclusion

In conclusion, this study provides the first analysis of *TPMT* mutant allele frequency in a sample of Jordanian population and indicates that *TPMT*3A* is the most common allele in Jordanian subjects while *TPMT*3C* is the least frequent.

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