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A Study of Cancer-Related Genes: Prevalence of Polymorphic GSTT1 and GSTM1 Deletions in Turkey

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Abstract

The major burden of cancer in the general population is results from the complex interactions of multiple genetic and environmental factors over time. Population based studies support the involvement of GSTM1 and GSTT1 deletion in susceptibility to commonly occurring forms of cancer. The aim of this study was to determine frequency of GSTM1 and GSTT1 deletion variants in Turkish population. Deletion polymorphisms were screened in a collection of samples n=507 for GSTM1 and n=464 for GSTT1. After isolation of DNAs from whole blood, sequences of interest were amplified and then analyzed by electrophoretic methods in the presence of positive and negative controls. Allele frequencies were detected as 52% for GSTM1 and 24% for GSTT1 deletion polymorphisms. The obtained frequencies were consistent with the values that reported for different populations. Cancer is a disease of the genome and identification of the genetic characteristics of healthy individuals is important in determining of current risks, developing of preventive health care models and medical follow-up programs to reducing risk of diseases. However, during the treatment process it allows the selection of optimal therapy.

Keywords: cancer genetics, GSTM1 and GSTT1 deletions

INTRODUCTION

Environmental and genetic factors play a critical role in a cancer etiology. Familial cancers cover only 10–15% of total cancers, and the remaining cancers are influenced by environmental factors, infections and lifestyle [1]. The other important factors are the genetic variations (copy number changes, deletions, mutations, single nucleotide polymorphisms) that directly or indirectly contribute to the susceptibility of many types of cancer [2].

Members of the GST family (EC 2.5.1.18) involved in regulation of individual's ability to metabolize environmental carcinogens and are candidate genes for cancer susceptibility [3, 4, 5, 6]. The frequencies of GSTM1 and GSTT1 deletion carriers were reported very high (i.e., 20-50%) in most population based studies [7]. Deletion variants are associated with a lack of enzyme function and carriers may have an impaired ability to metabolically eliminate carcinogenic compounds, may therefore be at increased risk of cancer.

It should be emphasized that over a third of cancer deaths worldwide are due to a potentially modifiable risk factors [8]. Modifiable lifestyle and defined genetic susceptibilities give us opportunity to determine the individuals who is at high risk of developing cancer. The information about allelic distribution of genes in a given population is also important for research, development and implementation of personalized health care models which may bring targeted preventative healthcare strategies. The aim of this study was to determine the frequencies of *GSTM1* and *GSTT1* deletion variants in Turkish population.

MATERIAL AND METHODS

Deletion polymorphisms were screened in a collection of samples n=507 for GSTM1 and n=464 for GSTT1 after obtaining the informed consent from volunteers applied to GENAR institute. Genomic DNAs were isolated from whole blood and sequences of interest were amplified using allele specific PCR primers. Amplicons were analyzed in the presence of positive and negative controls, using agarose gel electrophoresis.

RESULTS AND DISCUSSION

Multiple lines of evidence from molecular epidemiological studies suggest that GSTM1 and GSTT1 are involved in cancer susceptibility. We have reported here the frequencies of GSTM1 and GSTT1 deletion polymorphisms which associated with an increased risk of cancer. In most of population based studies the frequencies of homozygous GSTM1 and GSTT1 deletion carriers were reported very high (i.e., 20-50%) [4].

In this study allele frequency was detected as 52% for GSTM1 deletion polymorphism. It was found 42.1% in Brazilians [9], 46% in Americans [10], 49% in Polish [11], 51% in Swedish people [12]. The frequency of GSTM1 deletion across different populations is well summarized in Table 1 [13]. When we compare our results for the same variant, the values determined here is consistent with values obtained for many populations (Table 1). However, taking into account of potentially high attributable risk of GSTM1 deletion to the cancer, determined value (52%) in our population is noteworthy.

Table 1. Frequency of GSTM1 and GSTT1 null alleles across populations [10].

LOCUS	*FREQUENCY*	*POPULATION*
GSTM1	0,28-035	African American (US)
	0,22	African (Nigeria)
	0,67	Caucasian (Australia)
	0,38-0,62	Caucasian (European)
	0,49-0,54	Caucasian (US)
	0,35-0,63	Chinese (Asia)
	0,33-0,36	Indian (Asia)
	0,51	Japanese (US)
	0,53	Korean (US)
	0,59	Filipino (US)
	0,64-1,0	Pacific Islander
GSTT1	0,24	African American (US)
	0,38	African (Nigeria)
	0,16	Caucasian (Australia)
	0,11-0,18	Caucasian (European)
	0,16	Caucasian (US)
	0,58	Chinese (Singapore)

GSTT1 gene deletion was observed 24% in screened individuals. Our result is appearing to be higher when values determined in different societies were compared. The 14% of Americans [7], 20% of Swedish [9], 16% Australian Caucasians, 18% European Caucasians [10] were carriers of this variant. However, it is lower than frequency (over 50%) that reported for Asians. It has also been suggested that the high frequency of GSTT1 deletion allele is associated with the high incidence of esophageal cancer in China [14]. From Turkey there is a study that indicate association of this allele with a greater risk of colorectal cancer [15]

When frequencies for both GST variations were compared it seems that *GSTM1* gene deletion is more frequent in our population than GSTT1 deletion. As an illustration of the potential population impact of these genes, it has been estimated that 17% of lung and bladder cancers may be attributable to GSTM1 genotypes [16,17]. There are several reports from Turkey related GSTM1 and GSTT1 null genotypes involvement in different types of cancer. A contribution of GSTM1 "null" variants to the development of acute leukemias has already been reported [18]. The GSTM1 null genotype was found more prevalent in squamous-cell carcinoma and adenocarcinoma patients [19] and also suggested that it may significantly increase the risk of head/neck cancers [20]. Meta analysis of fifty studies with 10,805 cases and 13,332 controls found strong association between the combination of GSTT1 null and GSTM1 null genotype and risk of BC [6].

The potentially high attributable risk associated with GSTM1 or GSTT1 suggest that these genes are important candidates for studies that attempt to understand the complex and multifactorial etiology of cancer in the general population. However, studies that specifically evaluate the utility of these genotypes in cancer risk prediction have yet to be conducted. These studies will be crucial to establish the value of GSTM1 and GSTT1 in cancer prevention or control strategies. Our results will hopefully assist in the design of cancer related association studies in Turkey. Meantime, identification of the genetic characteristics of healthy individuals in a given population is important in determining of current risks, developing individualized nutritional, pharmacological and medical follow-up advice in accordance with the requirements of genetic background, to prompt preventive health care models, which allows reducing risk for complex diseases. However, during the treatment process it allows the selection of optimal therapy

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