RESEARCH ARTICLE

Association of TAP1 and TAP2 Gene Polymorphisms with Hematological Malignancies

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Abstract

Transporter associated with antigen presenting (TAP) 1 and TAP2 genes are localized in the major histocompatability complex (MHC) class II region and form a heterodimer playing a key role in endogenous pathways for antigen presentation. Defects of these genes have been reported to be common in different types of cancer. Polymorphisms identified in these loci have also been investigated and reported to be associated with several autoimmune disorders, viral infections and neoplasms. In the present study, for the first time, the allele and genotype frequencies of TAP1-333, TAP2-565, TAP2-651 and TAP2-665 were determined in patients with hematological malignancies (HM) using a PCR-RFLP method and compared with the frequencies in the control group. Our results suggested an association of TAP1-333 polymorphism with multiple myeloma-MM and TAP2-565 polymorphism with chronic lymphoid leukemia-CLL. In addition, it could be concluded that the TAP2-665 GG genotype might be a risk factor for all types of hematological malignancies included in this study.

Keywords: TAP1 - TAP2 - hematological malignancy - polymorphism - Turkish population

Asian Pac J Cancer Prev, **14 (9)**, 5213-5217

Introduction

Hematological malignancies (HM) comprise a collection of acute and chronic lymphoproliferative and myeloproliferative diseases, all originating from cells of the bone marrow and the lymphatic system. Leukemias, lymphomas, myeloma, myelodysplastic syndromes and myeloproliferative diseases are included in hematologic malignancies. Acute and chronic myelogenous leukemia, myelodyplastic syndromes and myeloproliferative diseases are derived from the myeloid line, while lymphomas, lymphocytic leukemias, and myelomas are lymphoid in origin. The classification of hematological malignancies is highly complex due to high level of heterogeneity with respect to clinical features and acquired genetic alterations. The combination of several features including the morphology of the tumor cells, immunophenotype, genetic abnormalities and clinical features are used for classification (Harris et al., 1999). The etiology of HM is largely unknown, but studies have indicated that exogenous toxicants such as; cytotoxic drugs, benzene, ionizing radiation and tobacco smoking may play an important role in the development these neoplasms (Descatha et al., 2005; Irigaray et al. 2007) but little is known about individual susceptibility to HMs.

Components of the antigen processing machinery (APM) and human leukocyte antigen (HLA) class I molecules play key roles in the endogenous antigen presentation and are therefore involved in immune recognition of virally infected and transformed cells (Heemels and Ploegh, 1995). The efficiency of peptide-HLA complex presentation on the cell surface depends on the production and processing of the peptide. Peptides generated as a result of degredation of intracellular proteins by proteasome are selected and transported to endoplasmic reticulum by the transporter associated with antigen processing (TAP) (Powis et al., 1993).

The TAP1 and TAP2 genes are members of the ATP-binding cassette (ABC) transporter superfamily and localized in MHC class II region, between the DQB1 andDPA1 loci. TAP1 and TAP2 proteins forms a heterodimer responsible for the transportation of antigenic peptides from the cytosol into the lumen of the endoplasmic reticulum prior to the assembly of class I molecules (Trowsdale et al., 1990). This HLA class I antigen-peptide complex is transported to the cell surface and is recognized by immune system as a signal of virus infection, cancer, or autoimmune disease (Spies et al., 1992).

The TAP1 and TAP2 genes were found to be polymorphic; seven TAP1 alleles and four TAP2 alleles have been officially named by World Health Organization HLA Nomenclature Committee (Marsh et al., 2005). TAP polymorphisms have been shown to influence the selection of peptide epitopes in rats (Momburg et al., 1994). Genetic variations in TAP1 or TAP2 genes may

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result in structural changes that prevent TAP heterodimer formation and alter antigen recognition and presentation (Koch et al., 2004). This may result in a failure of antigen presentation leading to low or no expression of MHC-I molecules on the cell surface and consequently an adverse affect in the immune response. Specificity can be affected by individual variability in structure and/or expression of these genes and therefore different sets of peptides could be derived from the same antigen being presented to T cells in different people. Thus, TAP genes are attractive candidates of disease susceptibility/severity factors (Vinasco et al., 1998).

Polymorphisms of TAP genes have been associated with various diseases such as tuberculosis (Wang et al., 2012), ankylosing spondylitis (Feng et al., 2009), leprosy (Shinde et al., 2013), idiopathic bronchiectasis (Dogru et al., 2007), cystic fibrosis (Ozbas-Gerceker et al., 2002) and also with the risk of occurence of several malignant tumors including colon cancer (Yang et al., 2005), cervical carcinoma (Mehta et al., 2007) and esophageal carcinoma (Cao et al., 2005). To the best of our knowledge there has been no study on the association of TAP gene polymorphisms with hematological malignancies. Therefore, in this study we have investigated a polymorphism (TAP1-333) in TAP1 gene and three polymorphisms (TAP2-565, TAP3-651, TAP2-665) in TAP2 gene in patients with hematological malignancies and control group.

Materials and Methods

Subjects

A total of 99 patients, consecutively diagnosed with a hematological malignancy (chronic myeloblastic leukemia-CML, chronic lymphoid leukemia-CLL and multiple myeloma-MM) at Gaziantep University Faculty of Medicine Department of Internal Medicine Section of Hematology, were included in the study. Patient distribution of the groups is as follows; 48 CML patients (15 males and 33 females aged between 19-78), 26 CLL patients (9 males and 17 females aged between 40-80) and 25 MM patients (15 males and 10 females aged between 36-74).

The control group consist of 100 unrelated healthy subjects with similar ethnic background and from the same geographic area of the patients (45 males and 55 females; aged between 19-80). Selection criteria for controls were no evidence of any personal or family history of cancer or other serious illness. Informed consent was obtained from each participant before blood sampling and the study was approved by the local Ethical Committee of Gaziantep University.

DNA extraction and genotyping

Blood samples were collected into ethylenediaminetetraacetic acid (EDTA) tubes. Genomic DNA was extracted using a standard salting-out procedure (Miller et al., 1988) and samples were stored in Tris EDTA buffer at -20ºC for subsequent analysis.

Genotyping for the TAP1 and TAP2 gene polymorphisms was performed by using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. Genomic DNA samples (0.25 mg) were amplified in 25 ml reaction mixtures containing 0.25 mg of each oligonucleotide primer, 200 mM dNTP's, 1Xtaq DNA polymerase buffer, and 0.5 units of Taq DNA polymerase (Fermentas, Lithuania). PCR was performed using a thermal cycler (Takara Bio Inc., Japan) by denaturing at 95°C for 5 min, followed by 35 cycles as denaturation at 94°C for 1 min, annealing at appropriate temperature for 2 min, extension at 72°C for 2 min, and the final extension at 72°C for 10 min. The amplified products were digested using specific restriction endonuclease under different conditions as per the manufacturer's instructions. After digestion, the fragments were electrophoresed in a 3% agarose gel and were visualized by ethidium bromide staining. The sequence of PCR primers and the restriction enzymes used for the genotyping are shown in Table 1. Re-genotyping of randomly selected samples was performed to confirm the results, and all the results were in agreement with the previous ones.

Statistical analysis

Genotype and allele frequencies of TAP1 and TAP2 polymorphisms were determined by direct counting and compared between control and patient groups using the chi-square test, and odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the relative risk conferred by a particular allele and genotype. Hardy-Weinberg equilibrium was also tested by chi-square analysis. Statistical significance was assumed at the $p<0.05$ level. The SPSS statistical software package version 13.0 was used for all of the statistical analyses.

Results

A total of 99 patients with hematological malignancies (CML, CLL, MM) and 100 healthy control subjects were investigated for TAP1333, TAP2565, TAP2651 and TAP2665 polymorphisms. Table 2 shows the distribution of the genotype and allele frequencies for TAP gene polymorphisms in the all studied groups. The result of the Hardy-Weinberg (HW) equilibrium test indicated that the genotypes in control and all patient groups were distributed as expected under HW equilibrium ($p>0.05$) (data not shown).

Comparison of the frequency of TAP1/TAP2 genotypes between HM (all) and control group

The difference in the genotype frequency of TAP1-333, TAP2-565 and TAP2-651 polymorphisms between HM cases (all) and control group was found to be non-significant. However, the genotype distribution of TAP2 665 site differed significantly between two groups. Compared to the TAP2-665 AA genotype, subjects carying the GG genotype had a significant 15.1-fold increased risk of hematological malignancy (95%CI 1.9-119.8, p=0.01).

The comparison of allele frequencies revealed that the frequency of TAP2-665 G allele was found to be 2.04-fold higher in HM cases than in the control group (OR=2.04, 95%CI 1.26-3.31, p=0.03).

Comparison of the frequency of TAP1/TAP2 genotypes between CML cases and control group

In addition to the HM (all) vs. control, each patient group was also compared to the control subjects with respect to each polymorhism. Of the total 99 HM subjects, 48 were diagnosed as CML. When the genotype distributions of polymorphisms were compared between control and CML cases, a significant difference was observed only in the frequency of TAP2-665 GG genotype. No statistically significant difference was found in the allele/genotype frequencies of TAP1-333, TAP2-565 and TAP2-651 sites between two groups (p>0.05).

The prevalence of TAP2-665 GG homozygote was significantly higher in the CML cases than in the control group (OR=10.5, 95%CI 1.12-98.0, p=0.04). The allele frequencies were also determined and compared between two groups. TAP2-665 G allele frequency was to be significantly higher in CML cases than in the control group (OR=1.88, 95%CI 1.05-3.37, p=0.03).

Comparison of the frequency of TAP1/TAP2 genotypes between CLL cases and control group

The comparison of the genotype frequency between CLL cases (n=26) and control group revealed no significant difference in the genotype distributions of TAP1-333 and TAP2-651 polymorphisms (p>0.05). The frequency of TAP2-565 GA heterozgygotes was found to be higher in CLL cases (15%) than in the control group (4%) (OR=4.36, 95%CI 1.01-18.8, p<0.05). Similarly, the prevalence of the TAP2-665 GG genotype was significantly higher in the CLL cases than in the control group (OR=22.7, 95%CI 2.46-208.4, p<0.01).

As shown in Table 2, the frequency of G allele in TAP2-665 site was significantly high in the CLL cases when compared with the control group (OR=2.25, 95%CI 1.12-4.52, p=0.02).

Comparison of the frequency of TAP1/TAP2 genotypes between MM cases and control group

No statistically significant differences were found in the allele/genotype frequencies of TAP2-565 and TAP2-651 polymorphisms between MM cases and the control group (p>0.05). However, the frequency of TAP1-333 AA genotype was significantly lower in MM cases than in the control group. Compared to AA genotypes, subjects carying the GG genotype had a significant 6.56-fold increased risk of MM (95%CI 1.24-34.7, p<0.01). Similarly, the prevalence of the AG genotype was significantly higher in MM cases (56%) than in the control group (26%) (OR=4.71, 95%CI 1.77-12.5, p<0.01). Comparison of the allele frequencies revealed that the frequency of G allele was significantly higher in MM cases than in the control group (OR=3.25, 95%CI 1.66-6.39, p<0.01).

The genotype distribution of TAP2-665 was compared and it was indicated that GG genotype frequency was significantly higher in MM (12%) than in the control group (1%) (OR=15.7, 95%CI 1.51-162.8, p=0.02) just as in HM (all), CLL and CML. The G allele was observed 2.17-fold more in MM cases than in the control group (95%CI 1.06-4.41, p=0.03).

Table 1. PCR Primers and Restriction Enzymes Used for the Analysis of TAP1 and TAP2 Polymorphisms

Polymorphism	Primer sequence	Enzyme
TAP1-333	F 5'- CACCCTGAGTGATTCTCT- 3'	Sau3A1
rs1057141	R 5'- ACTGACTCTGCCAAGTCT- 3'	
TAP2-565	F 5'-GGAGCAAGCTTACAATTTGTAGAAGATACC-3'	Sca1
rs2228396	R 5'- CTGTTCTCCGGTTCTGTGAGGAACAACAGT-3'	
TAP2-651	F 5'-GGTGTGAGGGCAGCCCCAGTTCCCT- 3'	Sma1
rs4148876	R 5'-ATCACCAGCACTGTGCGATCCCCCC- 3'	
TAP2-665	F 5'-GGTGATTGCTCACAGGCTGCCG- 3'	Msp1
rs241447	R 5'-CACAGCTCTAGGGAAACTC- 3'	

Discussion

Playing a key role in MHC class I molecule assembly and endogenous pathway for antigen presentation, TAP genes are strong candidates for disease susceptibility. The genetic variations located at TAP1 nad TAP2 gene coding regions may result in the structural and functional changes of the complex, which subsequently interferes with the

Table 2. Genotype and Allele Frequencies of TAP1 and TAP2 Polymorphisms in Hematological Malignancies and Controls

Genotype		Control n=100	Cases n=99	p*	OR* (95%CI)	CML n=48	p*	OR (95%CI)	CLL n=26	p*	OR (95%CI)	MM n=25	p*	OR (95%CI)
TAP1 333	AA	70	65		1.00**	38		1.00**	19		1.00**	8		1.00**
	AG	26	28	0.64	1.16 (0.62-2.18)	9	0.3	0.64 (0.27-1.50)	5	0.53	0.71 (0.24-2.09)	14	**<0.01**	**4.71 (1.77-12.5)**
	GG	4	6	0.47	1.61 (0.43-5.98)	1	0.49	0.46 (0.05-4.27)	2	0.5	1.84 (0.31-10.8)	3	**<0.01**	**6.56 (1.24-34.7)**
	A	166	158		1.00**	85		1.00**	43		1.00**	30		1.00**
	G	34	40	0.41	1.24 (0.75-2.05)	11	0.22	0.63 (0.30-1.31)	9	0.96	1.02 (0.46-2.29)	20	**<0.01**	**3.25 (1.66-6.39)**
TAP2 565	GG	96	94		1.00**	47		1.00**	22		1.00**	25		1.00**
	GA	4	5	0.72	1.28 (0.33-4.90)	1	0.55	0.51 (0.05-4.69)	4	**<0.05**	**4.36 (1.01-18.8)**	0	0.56	0.42 (0.02-8.06)
	AA	0	0	0.99	1.02 (0.02-51.9)	0	0.72	2.03 (0.04-103.9)	0	0.47	4.29 (0.08-222.0)	0	0.51	3.78 (0.07-195.4)
	G	196	193		1.00**	95		1.00**	48		1.00**	50		1.00**
	A	4	5	0.73	1.27 (0.34-4.79)	1	0.55	0.52 (0.06-4.68)	4	0.05	4.08 (0.98-16.9)	0	0.57	0.43 (0.02-8.16)
TAP2 651	CC	84	75		1.00**	36		1.00**	20		1.00**	19		1.00**
	CT	15	22	0.18	1.64 (0.79-3.39)	11	0.23	1.71 (0.72-4.09)	5	0.55	1.40 (0.45-4.31)	6	0.29	1.77 (0.61-5.15)
	TT	1	2	0.51	2.24 (0.20-25.2)	1	0.55	2.33 (0.14-38.3)	1	0.32	4.20 (0.25-70.1)	0	0.82	1.44 (0.06-36.8)
	C	183	172		1.00**	83		1.00**	45		1.00**	44		1.00**
	T	17	26	0.14	1.63 (0.85-3.10)	13	0.18	1.69 (0.78-3.63)	7	0.28	1.67 (0.65-4.28)	6	0.45	1.47 (0.55-3.94)
TAP2 665	AA	68	54		1.00**	26		1.00**	15		1.00**	13		1.00**
	AG	31	33	0.34	1.34 (0.73-2.45)	18	0.26	1.52 (0.73-3.17)	6	0.8	0.88 (0.31-2.48)	9	0.39	1.52 (0.59-3.93)
	GG	1	12	**0.01**	**15.1 (1.9-119.8)**	4	**0.04**	10.5 (1.12-98.0)	5	**<0.01**	**22.7 (2.46-208.4)**	3	**0.02**	**15.7 (1.51-162.8)**
	A	167	141		1.00**	70		1.00**	36		1.00**	35		1.00**
	G	33	57	**<0.01**	**2.04 (1.26-3.31)**	26	**0.03**	1.88 (1.05-3.37)	16	**0.02**	**2.25 (1.12-4.52)**	15	**0.03**	**2.17 (1.06-4.41)**

*Cases compared with controls; p-value<0.05, statistically significant; **Reference

immune response. TAP gene polymorphisms have been shown to be functionally effective in rats (Powis et al., 1992) but human studies revealed contradictory results. It was shown that human TAP1 polymorphism influenced the antigenic peptide transport in human lymphoblastoid and tumor cells (Quadri and Singal, 1998), while another in-vitro study showed no functional effect of TAP polymorphism (Daniel et al., 1997).

Previously, the frequencies of TAP1 and TAP2 gene polymorphisms were determined in healthy subjects from Anatolian population (Ozbas-Gerceker and Ozguc, 2003) and bronchiectasis (Dogru et al., 2007), cystic fibrosis (Ozbas-Gerceker et al., 2002) and cystic echinococcosis (Kiper et al., 2010) patients from Turkey. In the present study, we have investigated TAP1-333, TAP2-565, TAP2-651 and TAP2-665 polymorphisms in Turkish subjects to evaluate the association of these genetic variations with hematological malignancies. Our results suggest significant associations between TAP1-333, TAP2-565 and TAP2-665 polymorphisms and certain types of HM, but TAP2-651 could not be referred as a risk factor for HM.

The comparison of TAP1 333 allele and genotype frequencies in MM cases and control subjects indicated a marked increase of the G allele due to high prevelance of AG and GG genotypes in patients ($p<0.05$). The results of the present study suggest that subjects having homozygous AA genotype appear to be less susceptible to MM. In a previous study, it was suggested that positive association of genotype AG exist with the risk of bronchiectasis in children (Dogru et al., 2007). Besides, GG genotype was suggested to be a risk factor to develop tuberculosis (Sunder et al., 2011). G allele seems to contribute towards increased susceptibility to MM, similar to what we found in a study on Cystic Fibrosis (Ozbas-Gerceker et al., 2002). In a previous study, changes in expression of APM components (including TAP1 and TAP2) were shown to be associated with the progression of monoclonal gammopathy of undetermined significance (MGUS) to MM and it was hypothesized that aberrations in the expression of HLA class I APM components in transformed plasma cells distrupt the cells' ability to be recognized and killed by plasma cell-antigen specific cytotoxic CD8+ T cells residing in the bone marrow (Racanelli et al., 2011). It can be stated that the results of the present study support this hypothesis.

Another prominent result of this study is that; TAP2-565 genotype AA coding for Threonine was not detected in either the patient or control groups, which was also the case in several previous studies (Ozbas-Gerceker et al. 2002; Dogru et al., 2007; Shinde et al., 2013). The frequency of TAP2-565 heterozygous genotype GA was found to be significantly high in CLL cases compared to the control group ($p<0.05$) suggesting that this genotype could be a risk factor for the development of CLL. Genome wide association study conducted in CLL patients resulted in the identification of low-penetrance susceptibility loci but TAP genes were not defined as susceptibility loci for CLL (Di Bernardo et al., 2008). It could be argued that the clinical significance of these polymorphisms may likely vary depending on the disease context as well as on the allele distribution in a particular population.

TAP2-665 genotype GG seems to be a significant risk factor for the development of all HM types included in this study. Subjects having GG phenotype could be said to have a higher risk for different types of hematological malignancies compared to the ones carrying AA and AG genotypes.

TAP gene defects was found to be common (>50%) and correlate with progression in cervical carcinoma (Fowler and Frazer, 2004) and melanoma (Seliger et al., 2001; Dissemond et al., 2003). A high frequency of TAP1 down-regulation or loss was also found in tumor lesions and cell lines obtained from head and neck squamous cell carcinoma patients (Meissner et al., 2005). On the other hand, TAP gene defects were not seen in renal carcinoma (Hodson et al., 2003) and hepatocellular carcinomas (Deng et al., 2003) indicating that the selective pressure for TAP loss occurs not in all cancers but only in certain types. Adequate processing of endogenous tumor-associated proteins by APM and presentation of tumor derived epitopes by HLA class I molecules are required for the antitumor cytotoxic reactions in cell mediated immunity. Defects in the APM may contribute significantly to immune escape and persistence and as a result facilitate carcinogenesis.

Polymorphisms of TAP genes were investigated in many autoimmune disorders and infectious diseases as well as various malignancies and hypothesized to be important determinants of susceptibility to several viral infections and neoplasms. TAP gene polymorphisms were found to be associated with colon cancer (Yang et al., 2005), cervical carcinoma (Mehta et al., 2007) and esophageal carcinoma (Cao et al., 2005). However, literature rewieving yielded no specific study on the role of TAP polymorphisms in the pathogenesis of hematological malignancies. This is the first report announcing the association of specific TAP1 and TAP2 genotypes with HM. However, the exact role of TAP genes in the development of hematological malignancies remains to be investigated.

In conclusion, although the number of subjects included was small, this study demonstrated preliminary data for the role of TAP1 and TAP2 genes in the pathogenesis of hematological malignancies. Further studies with larger case and control groups are needed to confirm these findings. Identification of susceptibility genes may provide us better understanding of the mechanisms of hematological malignancies and also offer potential therapeutic targets.

Acknowledgements

The Authors thanks to the subjects participated in this study and Gaziantep University, Scientific Research Projects Governing Unit for the financial support.

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