RESEARCH ARTICLE

Possible Roles of the Xenobiotic Transporter P-glycoproteins Encoded by the *MDR1* 3435 C>T Gene Polymorphism in Differentiated Thyroid Cancers

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Abstract

Background: P-glycoprotein (Pgp), encoded by the multidrug resistance 1 (*MDR1*) gene, is an efflux transporter which plays an important role in pharmacokinetics. The current preliminary study was designed to determine associations between a germ-line polymorphism in the *MDR1* gene with differentiated thyroid carcinoma (DTC). Materials and Methods: In the current case-control study, 60 differentiated thyroid cancers (DTC)- 45 papillary TC (PTC), 9 follicular TC(FTC) and 6 well-differentiated tumors of uncertain malignant potential (WDT-UMP) were examined. Results were compared to a healthy control group (n=58) from the same population. Genomic DNA was extracted from peripheral blood with EDTA and the target gene was genotyped by real-time PCR. Results: Carriers of the variant allele of *MDR1* exon 26 polymorphism were at 2.8-fold higher risk of DTC than the control group (odds ratio [OR]: 0.3805, 95% confidence interval [Cl]: 0.1597-0.9065 (p> 0.046). Conclusions: Presented results suggest that the *MDR1* 3435TT genotype might influence risk of development of DTC and that the CC genotype might be linked to a poor prognosis. Large-scale studies are now needed to validate this association.

Keywords: Differentiated thyroid carcinoma - *MDR1* gene - increased T allele frequency in codon *C3435T*

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Introduction

The differentiated thyroid cancer (DTC), the most common type of all thyroid cancers accounts for >90%. It widely occurs in papillary and follicular types and its incidence has been increasing (Amrosini et al., 2011; Mondal et al., 2011; Sedov and Khmelevskaia, 2011; Caglar et al., 2012; Quan et al., 2012; Lerch and Richter, 2012). Early and/or late stage types of DTC may initiate by point mutations in different proto-oncogenes such as; *RET*, *B-RAF*, *NTRK1* and *K-RAS* (Moura et al., 2011; Namba et al., 2003), functional gene inactivation that is triggered by point mutations (Weier et al., 2009; Moses et al., 2010) and epigenetic alterations in some target genes (Sharma et al., 2010; Lu et al., 2011). Despite remarkable advances have occurred in recent years in understanding the etyopatogenesis of thyroid cancer, the exact molecular etiological mechanism still remain unclear. Papillary and follicular carcinomas commonly occur in one or more cervical lymph nodes that refer to as follicular cell-derived DTC of high percentage of all thyroid carcinomas. In general, DTC prognosis is easy for some patients but in a considerable number of patients, approximately 30%, have recurrent disease. The appropriate initial treatment which includes total thyroidectomy and radioiodine remnant ablation therapy with I-131 after thyroidectomy is a common application in patients with DTC (Kingpetch et al., 2011; Nixon et al., 2011; Zakani et al., 2011; Deandreis et al., 2012; Manduz et al., 2011).

It is well known that the toxic endogenous substances such as; drugs and xenobiotics are playing a crucial role in the development of cancer in different tissues. The P-glycoprotein (Pgp) is a ATP-dependent efflux transporter protein that is encoded by the multidrug resistance gene *MDR1* (*ABCB1*) and is expressed in many normal tissues such as; biliary ductiles, pancreas, kidneys, adrenal glands, choroid plexus of the brain, placenta and white blood cells regarding its multiple physiologic function. Functional protein plays an important role in transporting exogenous-endogenous substrates and xenobiotics, mediating cancer drug resistance across the blood-brain barrier. It is suggested that this transporter acts as a protective barrier to keep toxins out of the cell tissue and organs. The single nucleotide polymorphisms (SNPs) in *MDR1* gene may restrict intestinal absorption of various carcinogens, including heterocyclic amines

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(HCA) and polycyclic aromatic hydrocarbons (PAH) and may promote gastrointestinal carcinogenesis, affecting angiogenesis, apoptosis, and invasiveness as claimed by Andersen et al. (2009). Owing to the fact that it controls the efflux of toxic compounds, the Pgp transporter takes crucial role in the process of detoxification and elimination of xenobiotics which in turn is related to cancer risk (Andersen et al., 2009).

By the current case-control study we wished to explore the possible role of the xenobiotic transporter P-glycoprotein polymorphism (encoded by the *MDR1* gene) that is also known as the transport dietary carcinogen in the susceptibility of differentiated thyroid cancer.

Materials and Methods

Patients, clinical diagnosis and laboratory assessment

In a total of 60 thyroid cancer patients; 45 papillary thyroid cancer (PTC), 9 follicular thyroid cancer (FTC), 6 well-differentiated tumors of uncertain malignant potential (WDT-UMP) of 11 male (18.3%), 49 female (81.7%) and mean age-min-max; 55.25±3.22(28-75) were included in the current results. The PTC patients were include; 19 (42.2%) cases of conventional, 15 (33.3%) diffuse sclerosing variant, 7 (15.5%) follicular and 4 (8.8%) oncocytic subtypes of PTC patients. The current FTC pateints were include; 7 (77.7%) of conventional and 2 (32.3%) of Hurtle cell carcinomas histopathologically according to the WHO classification. Patients were genotyped for *MDR1 C3435T* SNP and compared to the healthy controls that are excluded from any familial cancer history. Results were compared to the 58 healthy control individuals from the same population that published in our previous case-control study (18).The volunteer individuals who has no any thyroid diseases were used as a control group cohort from the same population. There was no thyroid cancer history in those control cohort and their first degree relatives. The current study was performed in Departments of Nuclear Medicine and Medical Genetics of Cumhuriyet University Hospital between 2007-2009 years. All applications were approved and informed consent was obtained from all of the patients and control group individuals.

Mutation analysis

Blood samples with EDTA from 60 thyroid cancer patients that underwent total thyroidectomy were used in the current study. Total genomic DNA was extracted from peripheral blood samples from each individual by both automated Magna Pure Compact (Roche) and Invitek kit extraction techniques (Invitek®; Invisorb spin blood, Berlin, Germany) manually. Target *MDR1* gene was genotyped by Real Time PCR, LightCycler 2.0 methods (Roche) for all patients. Briefly, LightCycler FastStart DNA Master HybProbes, master mix (water, PCR-grade, $MgCl_2$, stock solution, Primer mix, HybProbe mix) and DNA template were used for real-time amplification. The protocol consisted of a denaturation step of 30 seconds at 95°C; followed by amplification step of 45 cycles of 5 seconds at 95°C, 5 seconds at 55°C, and 8 seconds at 72°C; and melting curve analysis of 30 seconds at 95°C, followed by 2 minutes at 40°C, 0.1 second (continuous) at 80°C, cooling step of 30 seconds at 40°C. Software programme (LightCycler 2.0, Roche) was used for detection of the mutated and normal genotype profiles of target gene in the current DTC patients.

Statistical analysis

In current results the odds ratio and p-values were used to estimate the risk for C, T alleles frequency of codon 3435 SNP for *MDR1* gene in DTC patients. The software SPSS for Windows version 12.0 was used to perform statistical analysis. Mutational variables were analyzed by using Fisher's exact test. The Mann–Whitney U and chi-square tests were used to analyze differences between the patients and the controls. The estimate risk was examined by multivariate logistic regression analysis. Results were given as the mean (standard deviation [SD]).

Results

In the current case-control study it was aimed to find out the association between germ-line point mutations in *MDR1* gene and thyroid carcinomas. By multiplex Real-time PCR technique, we evaluated common SNP 3435 C>T for *MDR1* gene in DTC patients and results were compared to the healthy controls (Figure 1). The estimate risk was examined by multivariate logistic regression analysis. Statistically, the TT homozygous genotype of polymorphic 3435 C>T SNP codon was associated with a significance of 2.8 fold increase in risk for DTC patients in the current results.

Clinicopathologic data and follow-up knowledge

Peripheral blood-EDTA samples from healthy controls and DTC patients were examined for genotyping in the current study. In a total of 60 DTC patients [(49F (81.7%) and 11M (18.3%)] of 45 PTC (75%), 9 FTC (15%) and 6 UMP (10%) mean age 55.25±13.22 (28-75) were clinically diagnosed and treated. The subtypes and some clinical characteristics such as; mean age, sex distribution of patients were given in Table 1. The

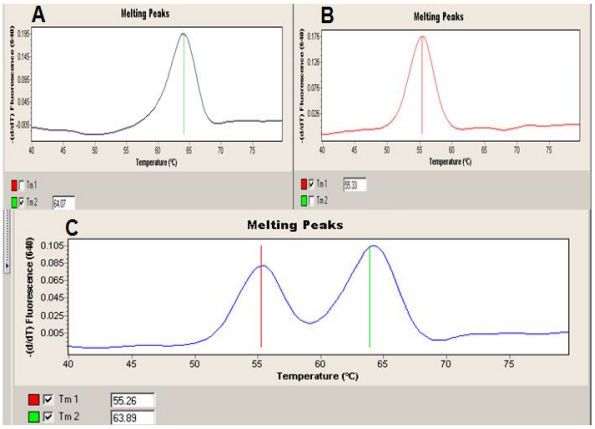

Figure 1. Shows Melting Peak Profiles of Real Time – PCR for wild (A) and Mutated Genotypes for *MDR1* 3435 C>T SNPs in the Current DTC Patients. B: Homozygous Mutated TT Alleles, C: Heterozygous CT alleles

genotype analysis and statistical results for *MDR1* 3435 C>T SNP were demonstrated in the Table 2. Studied DTC patients showed 26(43.4%) CC, 20(33.3%) CT and 14(23.3%) TT genotypes for 3435 C>T SNP (Figure 1), (Table 2). The C allele frequency was 0.600 and T allele frequency was 0.400 for studied SNP in DTC patients (Table 2). The frequencies of *MDR1* 3435 C/C, C/T, T/T in healthy controls were 41(70.69%), 12(20.69%), 5(8.63%) respectively, Elevated risk for DTC of 2.8 fold was observed in individuals with homozygous TT genotype odds ratio [OR]: 2.849, 95% confidence interval [Cl]: 1.578-5.142 (P<0.001) when compared to the healthy control group from the same population.

Multivariate analysis demonstrated the TT genotype, an increased risk of DTC for the 3435 C>T homozygous genotype for the presented results. The results indicated that individuals with homozygous TT genotype had a 14.67% higher risk of having DTC. The current results were also compared to the latest literature findings that showing the strong association of T allele frequency of *MDR1* gene in distinct tumoural types in different populations (Table 3).

Table 1. Shows Some Clinical Characteristics of Age, Gender and Tumour Types of Current Patients with Differentiated Thyroid Carcinomas

Clinical Characteristics		DTC Patients (n:60)	Control (n:58)
Tumour type		PTC FTC WDT-UMP -	
n(%)		45 (75%) 9 (15%) 6 (10%)	
Gender n(%)	F	49 (81.7)	20 (34.5)
	M	11 (18.3)	38 (65.5)
The mean age±SD		55.25±3.22	58.8±11.6
(Min-Max)		(28-75)	(38-67)

Table 2. Mutation Distribution, Genotype, and Allele Frequency of Codon 3435 C>T SNP of the *MDR1* Gene [P-glycoprotein, ATP-binding Cassette (ABCB1) Superfamily of Membrane Transporters] in the Current DTC Patients and Control Groups

Gene	*MDR1* (*ABCB1*)
Exon	26
SNP	Transition C>T
Codon	3435

Genotype	GROUPS DTC Patients (n=60) n (%)	Allele Frequency Control (n=58) n (%)
CC	26 (43.4)	41 (70.69)
CT	20 (33.3)	12 (20.69)
TT	14 (23.3)	5 (8.63)
	DTC Patients C T	Control C T
	0.600 0.400*	0.811 0.189
P value	<0.001	
Pearson Chi-Square	12,509	
OR/(CI 95%)	2.849 (1.578-5.142)	

*Significant, p<0.001

Table 3. The Latest Literature Findings about Strong Association of T Allele Frequency of *MDR1* Gene C>T SNP in Distinct Tumoural Types in Human in Different Populations

Cancer type	Population	Reference
Colorectal	The meta-analysis	[38]He et al, 2013
Colorectal	North German	[39]Campa et al, 2012
Breast	Canary Islands(Spain)	[40]Henríquez-Hernández, 2009
Gastric	Iranian	[33]Sabahi et al, 2010
Gastric	Chinese	[41]Li et al, 2011
Leukemia	Chinese	[42]Qian et al, 2012, [43]Ni et al, 2012
Ovarian	Japan	[44]Nakajima et al, 2005
Lung	Turkish	[45]Dogu et al, 2012
Hepatic	Chinese	[46]Huang et al, 2012
Other Common (Renal, Breast)	The meta-analysis	[47]Sheng et al, 2012, [48]Wang et al, 2012

*Significant: The status of T allele frequency for *MDR1* C>T SNP

Discussion

The incidence of refractory thyroid cancers including undifferentiated and differentiated cancers are increasing in several populations (Schlumberger et al., 2011). Wide range of genetic factors were reported in thyroid cancer susceptibility (Akdi et al., 2011; Schlumberger et al., 2011). The DTC is the most common malignancy of the thyroid gland and involves some molecular ethiological parameters such as; point mutations in proto-oncogenes of *BRAF* V600E, *KRAS*, *RET*, functional genes of *MTHFR*, *MDR1* and epigenetic alterations of several tumor suppressor gene abnormalities (Jasim et al., 2011; Jin et al., 2011; Ozdemir et al., 2012). Differentiated thyroid cancer (DTC) is an important clinical entity in our population which is characterized by important environmental influences, as iodine deficiency (ID) and subsequent supplementation, thyroiditis and occupational exposure. Thyroid cancers of follicular cell origin account for the majority (95%) of all thyroid cancers and represent the most common type of endocrine neoplasia. Morari et al. (2011) have suggested that the detection of NIS gene expression may help characterizing patient's risk and individuals with a poor response to therapy in DTC (Morari et al., 2011). The polymorphic *MDR1* gene includes 28 exonic subunits and it is highly variable between different ethnic groups and populations. The genotype and allele frequency of *MDR1* gene from Turkish subpopulation was found to be significantly different from some other populations such as; Han Chinese, Uygur Chinese, Kazakh Chinese, Indian, Malay, Japanese, Caucasian, and Ashkenazi Jewish (Gumus-Akay et al., 2010). Silent *C3435T* polymorphism which is located in exon 26 of gene induces a conformational change in P-glycoprotein due to the ribosome stalling during translation (Kroetz et al., 2003). Fung and Gottesman (2009) claimed that the polymorphic P-glycoprotein shows substrate specificity for transporting of Verapamil (Fung and Gottesman, 2009). Wang et al. (2005) reported that the silent *MDR1 C3435T* polymorphism leads to an unstable mRNA molecule and consequently, lower P-glycoprotein activity in the target tissues (Wang et al., (2005). The *MDR1*/*ABCB1* gene seems to play a role in early carcinogenesis by preventing apoptosis in tumor

cells as suggested by researchers (Johnstone et al., 2000; Nakano et al., 2003; Fantappie et al., 2007).

The *MDR1 C3435T* polymorphism in exon 26 has been extensively investigated in the variability in cancer risk and therapeutic outcome (Andersen et al., 2009; Jasim et al., 2011; Lu et al., 2011; Manduz et al., 2011). Lots of researchers claim that point mutation in *MDR1* causes lower *in vitro* P-glycoprotein activity, changes substrate specificity, and alters expression due to the following factors: a lower mRNA stability, protein folding and altered ability of tissues to remove toxins and properly metabolize anticancer drugs. That might help explain the initiate and develop of different types of cancer, as well as design appropriate therapies based on the particular genetic composition of the tumors (Kroetz et al., 2003; He et al., 2010). The polymorphic homozygous (T/T) genotype of *MDR1* gene showed a significant association with the incidence of gastric (Sabahi et al., 2010) and colorectal cancers (Andersen et al., 2009).

Pharmacogenomics and pharmacogenetics studies have revealed that mutated *MDR1* gene is associated with alteration in P-gp expression and function and associated with higher risk of clinical conditions. Rao et al. (2010) have claimed that *MDR1* TT genotype might influence the risk to develop an acute lympoblastic leukemia (ALL) due to the lower activity of eliminating antileukemic drugs such as; anthracyclines, daunorubicin, vincristeine, mitoxanthrone that lead to lower intra cellular drug concentrations and a poor prognosis in ALL (Rao et al. (2010). Huang et al. (2011) have reported that P-glycoprotein that is encoded by mutated *MDR1* gene may be implicated into the hematotoxicity of benzene. Subjects carrying *MDR1* 3435 T/T genotype may have a higher risk of benzene poisoning (Huang et al., 2011). Crouthamel et al. (2010) have reported a novel genetic variation of GT1292-3TG, (Cys431Leu) in *MDR1* gene in leukemia patients by the accumulation of the intracellular doxorubicin, vinblastine, and paclitaxel (Crouthamel et al., 2010). P-glycoprotein, highly restricts the entry of ivermectin into the brain by an ATP-driven efflux mechanism at the blood-brain barrier. In dogs with a homozygous *MDR1* TT mutation though, ivermectin accumulates in the brain and provokes severe signs of neurotoxicosis and even death (Geyer et al., 2009).

Recently, there are lots of crucial reports about *MDR1* gene polymorphism and distinct human cancers in the literature (Li et al., 2001; Nakajima et al., 2005; Henriquez-Hernandez et al., 2009; Ni et al., 2011; Campa et al., 2012; Dogu et al., 2012; Qian et al., 2012; Huang et al., 2012; Sheng et al., 2012; Wang et al., 2012; He et al., 2013), (Table 3). We found that the functional SNP of *MDR1* gene was associated with DTC risk in the Turkish population. The current preliminary results on *MDR1* mutability on thyroid cancer are the first literature findings that showing mutation prevalence of the multidrug resistance *MDR1* (*ABCB1*) gene in DTC.

In the current preliminary study it was aimed to find out the possible linkage between homozygous mutated (T/T alleles) *MDR1* gene and DTC. Genomic DNA was extracted from peripheral blood and genotyped by Real Time PCR method. Presented results are the first report the genotype and allele frequency of polymorphic codon 3435 of *MDR1* gene in Turkish DTC patients. Preliminary results of the current study showed that homozygous T allele in 3435 C>T codon in *MDR1* gene may be associated with high risk of thyroid cancer and may play a pivotal role in the development of DTC in human. Despite some limitations, current results indicated that individuals with homozygous TT genotype had a 14.67% higher risk of having DTC. Furthermore, patients carrying both copies of the variant alleles (TT) showed 2.8 times increased risk of developing DTC than their control counterparts. By the presented case-control results it is possible to claim that the polymorphic xenobiotic transporter P-glycoprotein (encoded by the *MDR1* gene) which is also known as the transport dietary carcinogen is associated with susceptibility of DTC.

In conclusion, the codon 3435 C>T transitional polymorphism in exon 26 of *MDR1* gene was significantly associated with DTC risk in the current results. Results need to be supported by population based large–scale samples of representative DTC patients.

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