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N-acetyltransferase 2 gene polymorphisms and susceptibility to prostate cancer: a pilot study in the Turkish population

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Aim: To investigate the association between the 3 most frequently observed single nucleotide polymorphisms of the *NAT2* gene and the risk of developing prostate cancer in the Turkish population.

Materials and methods: A total of 110 unrelated patients with prostate cancer were included in this case-control association study and constituted the study group. The control group also consisted of 150 unrelated but healthy men. Genomic DNA was isolated from peripheral blood leukocytes of all patients and analyzed with a sensitive real-time PCR method. After melting curve analysis genotypes were identified for the *NAT2*5A*, *NAT2*6A*, and *NAT2*7A/B* polymorphisms.

Results: Prostate cancer patients had a higher frequency of the mutant *NAT2*6A* (13.6% versus 4.0%, P = 0.009) and heterozygote *NAT2*7A/B* (20.9% versus 9.3%, P = 0.008) genotypes when compared with the controls.

Conclusion: The *NAT2*6A* and *NAT2*7A/B* gene polymorphisms were significantly associated with prostate cancer in the Turkish population. Real-time PCR analysis of the *NAT2* acetylator phenotype can therefore be used to recognize individuals with a high risk of developing prostate cancer.

Key words: *N*-Acetyltransferase 2, prostate cancer, acetylator phenotype

N-acetyltransferase 2 gen polimorfizmleri ve prostat kanserine yatkınlık: Türk populasyonunda pilot bir çalışma

Amaç: Bu çalışmanın amacı *NAT2* geninde en sık gözlenen 3 tek nükleotid gen polimorfizmi ve prostat kanseri gelişme riski arasındaki ilişkinin Türk toplumunda araştırılmasıdır.

Yöntem ve gereç: Akraba olmayan toplam 110 prostat kanserli olgu bu çalışmaya dahil edilmiş ve çalışma grubunu oluşturmuştur. Kontrol grubu yine akraba olmayan 150 sağlıklı erkek olgudan oluşturulmuştur. Bütün olguların genomik DNA' ları periferik kan lökositlerinden izole edilmiş ve oldukça duyarlı gerçek-zamanlı bir PCR yöntemi ile analiz edilmiştir. *NAT2*5A, NAT2*6A* ve *NAT2*7A/B* polimorfizmleri için genotipler erime eğrisi analizinden sonra belirlenmiştir.

Bulgular: Prostat kanserli olgularda mutant *NAT2*6A* (%13,6' ya karşı % 4,0, P = 0,009) ve heterozigot *NAT2*7A/B* (% 20,9' a karşı % 9,3, P = 0.008) genotiplerinin sıklıkları kontrol grubu ile karşılaştırıldıklarında daha yüksek bulunmuştur.

Sonuç: *NAT2*6A* ve *NAT2*7A/B* gen polimorfizmleri Türk toplumunda prostat kanseri ile anlamlı şekilde ilişkili bulunmuştur. Buna göre yüksek risk taşıyan bireylerin *NAT2* asetilatör fenotipinin belirlenmesi için gerçek-zamanlı PCR analizi kullanılabilir.

Anahtar sözcükler: *N*-Asetiltransferaz 2, prostat kanseri, asetilatör fenotipi

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Introduction

In the United States of America prostate cancer is the most commonly diagnosed cancer in men, whereas in Turkey it ranks fourth (1). Today it is widely accepted that age, ethnical differences, and genetic factors have a significant impact on its etiology. Epidemiological studies have shown that also environmental factors like ultraviolet irradiation (2) and differences in life style like smoking (3) and nutrition, especially dietary lipids and their way of preparation (4), have some effects on prostate cancer development as well.

The bioactivation or inactivation processes of many chemicals and carcinogens as nitrosamines and arylamine amines, that are formed after lipid metabolism or are found in cigarette smoke, are controlled by enzymes. If these carcinogens are metabolically active they can initiate carcinogenesis by damaging DNA (5). Through *N*-oxidation or *O*-acetylation by *N*-Acetyltransferase (NAT) enzymes *N*-hydroxy aromatic and heterocyclic amines are activated to acetoxy intermediary compounds, which can bind to DNA and produce adducts (6). It was reported that prostate epithelial cells express phase II metabolizing NAT enzymes and that they can metabolize potential carcinogens (7,8).

NAT2 plays an important role in the activation and inactivation processes of many drugs and carcinogenic chemicals. Its gene is quite polymorphic and some of these polymorphisms can affect enzyme activity; e.g., 2 or more polymorphisms result in a slow acetylator phenotype, whereas a heterozygote or wild type genotype results in a rapid or medial acetylator phenotype (6,9). Consequently, the acetylation ratio of drugs and carcinogens can change with respect to an individual's acetylator phenotype and predispose them to diseases like cancer.

The aim of this study was to determine the association between 3 frequently observed single nucleotide polymorphisms of the *NAT2* gene and the risk of developing prostate cancer in the Turkish population.

Materials and methods

Subjects

A hundred and ten patients operated on for clinically organ confined prostate cancer were evaluated. Patients that had other than prostate adenocarcinoma were not included in this study. Serum PSA, Gleason score of the surgical specimen, and pathological stage were determined as study group parameters (Table 1).

The control group was established with 150 unrelated healthy men. Attention was paid that they fell into the same age interval as the study group patients. If there was any suspicion of prostate cancer regarding the rectal digital examination or serum total prostate specific antigen (PSA) value, these patients were excluded from the study.

Our study protocol was approved by the Ethical Committee of Ege University Faculty of Medicine and signed informed consent from all participants was obtained.

NAT2 Genotype analysis

Genomic DNA from peripheral blood leukocytes of all patients was extracted with the High Pure PCR Template Preparation kit (Roche Applied Science, Germany). Genotyping of the subjects for the *NAT2*5A*, *NAT2*6A*, and *NAT2*7A/B* polymorphisms was performed by a real-time PCR method using the LightCycler® v2.0 instrument (Roche Applied Science, Germany). For this purpose, specific primers and hybridization probes (Tib Molbiol, Germany) for each analyzed polymorphism were used in combination with the LightCycler DNA Master Hybridization Probes kit (Roche Applied Science, Germany). Wild type, heterozygote, and mutant polymorphic genotypes were identified by specific melting temperatures (Tm) of the resulting amplicons (Table 2). Rapid or slow acetylator phenotype assignments were deduced on the basis of the *NAT2* genotype (10). Accordingly, genotypes possessing 2 or more polymorphic alleles (*NAT2*5, NAT2*6*, or *NAT2*7A/B*) were assigned as slow acetylator phenotypes, whereas those with 1 polymorphic or 2 wild type alleles were assigned as rapid acetylator phenotypes.

Statistical analysis

To test for the Hardy-Weinberg equilibrium expected genotype numbers were calculated from the allele frequencies. Deviation from the observed genotype numbers was determined by the chi-square test. For statistical analysis SPSS v15.0 for Windows was used. Differences in genotype prevalence and association between the study and control groups were assessed by a binary logistic regression model. P < 0.05 was considered statistically significant.

Results

The median age of the study and control groups was 65.18 ± 8.74 and 62.15 ± 9.15, respectively (Table 1).

Allele distribution was consistent with the Hardy-Weinberg equilibrium for all *NAT2* polymorphisms genotyped. Genotype analysis revealed that prostate cancer patients had higher frequencies of the mutant *NAT2*6A* (13.6% versus 4.0%, P = 0.009) and heterozygote *NAT2*7A/B* (20.9% versus 9.3%, P = 0.008) genotypes when compared with the controls. Comparisons of genotype distributions and allele frequencies of the *NAT2* polymorphisms between the study and control groups are shown in Table 3.

A significant higher frequency of the *NAT2* slow acetylator phenotype was observed in the study group when compared with the control group (49.1% versus 30.7%, *P* = 0.003, OR: 0.459, 95% CI: 0.27-0.76; Table 4).

The study group subjects had a wide range of PSA ranks, and so we considered the mean and median level when we compared PSA with the *NAT2* genotypes (Table 5). For the *NAT2*7A/B* polymorphism, the PSA levels were higher in the mutant genotype than in the heterozygote genotype.

No associations were found between tumor grades and *NAT2* genotypes (Table 6); but subjects with a heterozygote *NAT2*7A/B* genotype had a higher Gleason score (Table 7).

Table 1. Clinical characteristics of the study and control groups.

	Study group		Control group
	n	%	*n*
Total number	110		150
Age (years)	65.18 ± 8.74†		62.15 ± 9.15
PSA (ng/mL)			2.02 ± 1.7†
< 4	5	4.5	
4-12	62	59.0	
≥ 12	38	36.2	
T Stage I	6	5.5	
II	57	51.8	
III	31	28.2	
IV	16	14.5	
Gleason Score			
6	39	35.5	
7	43	39.1	
8	16	14.5	
9	12	10.9	

† Mean ± Standard Deviation

Table 2. Characteristics of the NAT2 polymorphisms and specific melting temperatures determined after melting curve analysis.

Polymorphism	*rs* number	Base change	Aminoacid change	Tm (°C)
*NAT2*5A*	1799929	C481T	Ile^{114}→Ile	WT: 49.00 Het: 49.00 + 57.50 Mut: 57.50
*NAT2*6A*	1799930	G590A	Arg^{197}→Gln	WT: 67.50 Het: 62.00 + 67.50 Mut: 62.00
*NAT2*7A/B*	1799931	G857A	Gly^{286}→Glu	WT: 66.00 Het: 62.00 + 66.00 Mut: 62.50

Tm : Melting Temperatures, WT: Wild type, Het: Heterozygote, Mut: Mutant

Table 3. Genotype distributions and allele frequencies of the NAT2 polymorphisms in the control and study groups.

Polymorphisms	Genotype Haplotype	Control N = 150 n (%)	Study N = 110 n (%)	P	OR†	95% CI‡
*NAT2*5A*						
(C481T)	CC	72 (48.0)	47 (42.7)	0.327	R§	
	CT	68 (45.3)	50 (45.5)	0.652	0.888	0.53-1.49
	TT	10 (6.7)	13 (11.8)	0.135	0.502	0.20-1.24
	C	212 (70.7)	144 (65.5)	0.206	0.786	0.54-1.14
	T	88 (29.3)	76 (34.5)			
*NAT2*6A*						
(G590A)	GG	91 (60.7)	60 (54.5)	**0.029**	R§	
	GA	53 (35.3)	35 (31.8)	0.995	0.998	0.58-1.71
	AA	6 (4.0)	15 (13.6)	**0.009**	0.264	0.10-0.72
	G	235 (78.3)	155 (70.5)	**0.04**	0.66	0.44-0.98
	A	65 (21.7)	65 (29.5)			
*NAT2*7A/B*						
(G857A)	GG	136 (90.7)	87 (79.1)		R§	
	GA	14 (9.3)	23 (20.9)	**0.008**	0.389	0.19-0.80
	AA	-	-			
	G	286 (95.3)	197 (89.5)	**0.011**	0.419	0.21-0.83
	A	14 (4.7)	23 (10.5)			

†Odds ratio, ‡Confidence interval, §Reference genotype

Table 4. Frequencies of the acetylator phenotypes in the study and control groups.

Acetylator Group	Control N = 150 n (%)	Study N = 110 n (%)	P	OR†	95% CI‡
Rapid	104 (69.3)	56 (50.9)	0.003	0.459	0.27-0.76
Slow	46 (30.7)	54 (49.1)			

†Odds ratio, ‡Confidence interval

Table 5. Relationship of the NAT2 genotypes with PSA levels.

Polymorphism	Genotype	n	PSA* (Mean**)	PSA* (Median)	P
*NAT2*5A (C481T)*	CC	47	13.5 ± 20.5	8.0	0.175
	CT	50	17.3 ± 19.6	10.1	
	TT	13	28.0 ± 50.1	9.6	
*NAT2*6A (G590A)*	GG	60	19.3 ± 28.8	10.5	0.054
	GA	35	16.3 ± 24.1	8.0	
	AA	15	8.9 ± 5.5	6.9	
*NAT2*7A/B (G857A)*	GG	87	12.1 ± 9.7	8.0	**0.003**
	GA	23	35.4 ± 48.8	17.6	

* *ng/mL,* ** ± Standard deviation

Table 6. Genotype distributions of the NAT2 polymorphisms and tumor grades in the study group.

Polymorphism	Genotypes	Tumor Grade				P
		I*	II*	III*	IV*	
*NAT2*5A (C481T)*	Wild type	4 (8.5)	23 (48.9)	13 (27.7)	7 (14.9)	0.457
	Heterozygote	2 (4.0)	29 (58.0)	14 (28.0)	5 (10.0)	
	Mutant	-	5 (38.5)	4 (30.8)	4 (30.8)	
*NAT2*6A (G590A)*	Wild type	2 (3.3)	30 (50.0)	20 (33.3)	8 (13.3)	0.703
	Heterozygote	2 (5.7)	19 (54.3)	8 (22.9)	6 (17.1)	
	Mutant	2 (13.3)	8 (53.3)	3 (20.0)	2 (13.3)	
*NAT2*7A/B (G857A)*	Wild type	6 (6.9)	47 (54.0)	22 (25.3)	12 (13.8)	0.337
	Heterozygote	-	10 (43.5)	9 (39.1)	4 (17.4)	
	Mutant	-	-	-	-	

* n (%)

Table 7. Genotype distributions of the NAT2 polymorphisms and Gleason scores in the study group.

Polymorphism	Genotypes	Gleason Score				P
		6*	7*	8*	9*	
*NAT2*5A (C481T)*	Wild type	17 (36.2)	18 (38.3)	8 (17.0)	4 (8.5)	0.936
	Heterozygote	19 (38.0)	19 (38.0)	6 (12.0)	6 (12.0)	
	Mutant	3 (23.1)	6 (46.2)	2 (15.4)	2 (15.4)	
*NAT2*6A (G590A)*	Wild type	16 (26.7)	28 (46.7)	9 (15.0)	7 (11.7)	0.129
	Heterozygote	18 (51.4	8 (22.9)	4 (11.4)	5 (14.3)	
	Mutant	5 (33.3)	7 (46.7)	3 (20.0)	-	
*NAT2*7A/B (G857A)*	Wild type	34 (39.1)	35 (40.2)	13 (14.9)	5 (5.7)	**0.008**
	Heterozygote	5 (21.7)	8 (34.8)	3 (13.0)	7 (30.4)	
	Mutant	-	-	-	-	

* n (%)

Discussion

Heterocyclic amines like PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) and MeIQx (2-amino-3,8-dimethylimidazo[4,5- f]quinoxaline) are formed when meat is cooked at high temperatures. They can induce tumor development in several organs (5). Therefore, humans eating cooked meats are exposed to those heterocyclic amines. Wang et al. showed that *NAT* transcripts are expressed in normal prostate cells and that these cells are capable in activating *N*-hydroxy compounds produced from heterocyclic amines (7). For this reason heterocyclic amines are potential carcinogens for the human prostate and cooked meat, which is a traditional food in Turkey, might constitute a risk factor for prostate cancer development. Other factors like tobacco smoking and alcohol consumption might even increase the risk of developing prostate cancer, but could not be assessed in this present study due to high variations in usage between the individuals.

It is well established that polymorphic differences in genes encoding metabolizing enzymes can also constitute risk factors for prostate cancer development (11). Al-Buheissi et al. showed that phase II metabolizing enzymes are expressed in human prostate cells and that they are able to catalyze the activation of an *N*-hydroxy metabolite of MeIQx that reacts with DNA and produces MeIQx-DNA adducts with marked interindividual variation in both expression levels and catalytic capability (12). The effects of *NAT2* gene polymorphisms on the catalytic activity of the resulting enzyme have been investigated primarily in recombinant expression systems. In humans *NAT2* polymorphisms can reduce substrate affinity, catalytic activity, and/or protein stability of the recombinant NAT2 allozymes. Recombinant human *NAT2*5A*, *NAT2*6A*, and *NAT2*7A* clusters give rise to a slow acetylator phenotype and to variable reductions in catalytic enzyme activity (13,14).

Although the acetylator status of *NAT2* in prostate (15,19), colorectal (20, 21), urothelial (22,23), and oral (24) cancers was investigated in several studies, the results were conflicting as to whether the slow or rapid acetylator status did constitute a risk factor. These inconsistencies can be explained by the fact that the *NAT2* allele distribution can vary between interethnic populations (6), as well as to exposure to environmental factors, which depends on the level of economic development of a country. Another fact is that the *NAT2* gene is quite polymorphic and not all polymorphisms were analyzed at the same time in these studies. Only the most frequently observed

polymorphisms, which can alter the acetylator status, were chosen. Lastly, different groups used various acetylator phenotype detection methods; e.g., the acetylator phenotype can be measured by a caffeine excretion method (25,26). However, this method is influenced by drugs (6,27), liver diseases (28), or foods (29), and could yield false results.

The *NAT2* acetylator phenotype should preferentially be determined by molecular biological tests. We used a real-time PCR method and detected the *NAT2*5A*, *NAT2*6A*, and *NAT2*7A* polymorphisms after melting curve analysis. During this analysis the LightCycler Instrument monitors the temperature-dependent hybridization of the sequence-specific Hybridization Probes to single stranded DNA. No post-PCR processing is needed and the risk of contamination is minimized, as amplification and genotyping are performed in the same sealed capillary without any further handling steps. This method is more expensive but very specific and more reliable than conventional PCR and restriction fragment length polymorphism (RFLP) analysis (30).

Hamasaki et al. found that the frequency of cases with a slow acetylator genotype was significantly higher in the prostate cancer group (OR = 2.21), associated with a more advanced stage of disease (T3/T4/N1/M1; OR = 3.14) and a higher pathological stage of tumor (OR = 4.90) (19). The mutant *NAT2*6A* genotype was also found in a higher frequency in prostate cancer cases compared with controls in the South European population (OR: 0.31, 95% CI: 0.11-0.84, P = 0.017) (17).

Srivastava et al. observed a non-significant association of the rapid *NAT2* acetylator genotype (OR = 1.452, 95% CI: 0.54-1.87, P = 0.136) in prostate cancer patients with a North Indian origin (18). However, when they analyzed the rapid *NAT2* acetylator genotype in prostate cancer patients that smoked tobacco (OR = 3.43, 95% CI: 1.68-7.02, P < 0.001) the association became more evident compared to the controls. On the other hand, Wadelinus et al. reported a non-significant association of the slow *NAT2* acetylator genotype with prostate cancer in the Swedish and Danish populations (16).

We found that Turkish prostate cancer patients had higher frequencies of the mutant *NAT2*6A* and heterozygote *NAT2*7A/B* genotypes when compared with the controls. Moreover, a significant higher frequency of the *NAT2* slow acetylator phenotype was observed in the study group when compared with the control group. Slow acetylator genotype could cause slow detoxification of carcinogens and lead to accumulation of them. Moreover, in patients with the mutant *NAT2*7A* genotype the PSA levels were higher compared with patients with a heterozygote genotype.

In conclusion, the *NAT2*6A* and *NAT2*7A/B* polymorphisms are significantly associated with prostate cancer in the Turkish population and a real-time PCR analysis of the *NAT2* acetylator phenotype can be used to determine subjects with a high risk of developing prostate cancer.

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