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TOXICOKINETICS AND METABOLISM

Genotype and allele frequencies of polymorphic *CYP2E1* in the Turkish population

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Abstract Cytochrome *P4502E1* (*CYP2E1*) gene shows genetic polymorphisms that vary markedly in frequency among different ethnic and racial groups. We studied the genotype distributions and allele frequencies of three *CYP2E1* polymorphisms: *CYP2E1*5B* (RsaI/PstI RFLP, C-1053T/G-1293C SNP, rs2031920 /rs3813867), *CYP2E1*6* (*Dra*I RFLP, T7632A SNP, rs6413432), and *CYP2E1*7B* (*Dde*I RFLP, G-71T SNP, rs6413420) by PCR/RFLP technique in a sample of 206 healthy subjects representing Turkish population. *CYP2E1*5B* polymorphism analysis yielded the genotype distribution as 96.12% for **1A/*1A* (c1/c1), and 3.88% for **1A/*5B* (c1/c2). The genotype frequencies for *CYP2E1*6* polymorphism were found as 83.98% for **1A/*1A* (T/T), 15.53% for **1A/*6* (T/A) and 0.49% for **6/*6* (A/A). For *CYP2E1*7B* (G-71T) polymorphism, the genotype frequencies were determined to be 86.89% for **1A/*1A* (G/G), 12.62% for **1A/*7B* (G/T) and 0.49% for **7B/*7B* (T/T). Accordingly, the allele frequencies for **5B, *6* and **7B* were 1.94, 8.25, and 6.80%, respectively. The genotype distributions of *CYP2E1*5B* and **6* in Turkish population were similar to those in other Caucasian populations, while differed significantly from East Asian populations. Recently, a novel and functionally important *CYP2E1*7B* polymorphism was identified in the promoter region. There have been few studies and limited data on *CYP2E1*7B* polymorphism frequency in the world and, so far, no information has been available for Turkish population. The genotype frequencies of *CYP2E1*7B* in Turkish population were found to be similar to those of other Caucasian populations. Population studies like this could be useful in assessing the susceptibility of different populations to chemical-induced diseases, including several types of cancer.

Keywords *CYP2E1* gene · Turkish population · Genetic polymorphism · Allele frequencies · *CYP2E1*5B, *6, *7B*

Introduction

Cytochrome P450-dependent monooxygenases exist as a large superfamily of proteins and are the principal enzymes involved in the phase I metabolism of foreign compounds including drugs, food additives, industrial solvents, and pollutants (Lu and Levin 1974; Arinç and Philpot 1976; Arinç and Adali 1983; Lieber et al. 1997). Besides detoxification, they often catalyze the metabolic activation of procarcinogens to their ultimate carcinogenic forms. As is the case for most of the xenobiotic-metabolizing enzymes, cytochrome P450s also show genetic polymorphisms which may alter the expression levels or activities.

Among the various P450s, CYP2E1 is of great interest due to its role in the metabolism and bioactivation of many low molecular weight compounds, including ethanol, acetone, drugs like acetaminophen, isoniazid, chlorzoxazone and fluorinated anaesthetics, and many procarcinogens like benzene, *N*-nitrosodimethylamine (NDMA) and styrene (Peter et al. 1990; Guengerich et al. 1991; Kharasch and Thummel 1993). Besides, CYP2E1 isoform is induced by ethanol, benzene, pyridine and isoniazid (Koop and Casazza 1985; Johansson and Ingelman-Sundberg 1988;

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Arinç et al. 2000a, b) as well as by some pathophysiological conditions like diabetes, obesity and starvation (Koop and Casazza 1985; Hong et al. 1987; Song et al. 1987; Arinç et al. 2005, 2007). *CYP2E1* gene (Accession No. AL161645) shows genetic polymorphisms which are thought to play a major role in interindividual variability in drug response, drug–drug, drug–xenobiotic interactions and in susceptibility to chemical-induced diseases (Lieber 1997; Bolt et al. 2003). Several reports demonstrated that *CYP2E1* polymorphisms differ markedly in frequency among different ethnic and racial groups, like most other xenobiotic-metabolizing enzymes do (Garte et al. 2001).

The human *CYP2E1* gene is located in 10q24.3-qter region of chromosome 10, and spans 11,413 base pairs with nine exons and a typical TATA box (Umeno et al. 1988). The gene contains several polymorphisms, some of which seem to effect the expression of the protein. Among *CYP2E1* polymorphisms, the most frequently studied ones are the *CYP2E1*5B* (*Rsa*I/*Pst*I RFLP; position:C-1053T/G-1293C, rs3813867/rs2031920) polymorphism located in the 5′-flanking region of the gene, which was related to altered enzyme expression in vitro (Hayashi et al. 1991); and *CYP2E1*6* (*Dra*I RFLP; position T7632A, rs6413432) polymorphism located in intron 6 (Uematsu et al. 1991), which was shown to lower 'chlorzoxazone metabolic ratios' (Haufroid et al. 2002), and was correlated with single strand breaks in DNA (Vodicka et al. 2001). Several case-control studies have described the influence of these polymorphisms with increased risk for various cancer types in different populations (El Zein et al. 1997; Wu et al. 1998; Farker et al. 1998; Liu et al. 2001).

In order to clarify the role of *CYP2E1* polymorphisms in disease/cancer susceptibility, the allele frequencies of these polymorphisms in control populations should be verified by several studies, since, in general, a sample size of only 100–300 subjects has been used in these polymorphism studies. Thus, each study on control populations would add data to the pool, which makes it possible to more precisely define the true population-frequency of polymorphisms in control populations. Garte et al. (2001) analyzed the allele and genotype frequencies of eight metabolic genes from the data obtained for a total of 73 separate studies gathered after 1996 covering nearly 16,000 control subjects. It has also been observed that different groups of investigators reported different frequencies for the same gene in the same population. For example, GSTT1 null frequency was reported to be 30% (Peter et al. 1989) and 19.5% (Garte et al. 2001) for German population. Another example is related to GSTM1 null frequency in Turkish population which was reported to be 16% by Pinarbasi et al. (2001), 37.4% by Aktas et al. (2001), 54.6% by Balta et al. (2003), and 51.9% by Ada et al. (2004). Therefore, it is of crucial importance to verify the genotype frequencies even in the same population.

While the frequencies of mutant alleles of drug metabolizing enzymes like GSTT1, GSTM1, CYP1A1 and CYP2C9 (Aynacioglu et al. 1999; Pinarbasi et al. 2001; Aktas et al. 2001; Balta et al. 2003; Ada et al. 2004) have been studied relatively extensively in Turkish population, only limited information is available for CYP2E1 polymorphisms (Omer et al. 2001).

Furthermore, Fairbrother and co-workers have detected another novel polymorphism of *CYP2E1* gene -the *Dde*I (mutated allele: *CYP2E1*7B*, G-71T, rs6413420) polymorphism located in the promoter region. Hence, it is suspected to be associated with the expression or regulation of the gene (Fairbrother et al. 1998). So far, studies and data regarding this polymorphism are very limited in the world. No information is available for the frequency of this *CYP2E1*7B* (G-71T) allele for the Turkish population.

We report here the genotype and allele frequencies of three *CYP2E1* polymorphisms, namely *CYP2E1*5B, *6* and **7B*, in a sample of 206 healthy subjects representing the Turkish population.

Materials and methods

Subjects

The study sample included a total of 206 healthy and unrelated Turkish volunteers between the ages of 12 and 65 years and mean age of 31.5 ± 12.0 years, including 125 females (mean age 30.4 ± 11.6 years; range 12–63 years) and 81 males (mean age 33.1 ± 12.7 years; range 14–65 years), without known history of cancer and other chronic diseases. Venous blood from the participants was collected with the collaboration of Middle East Technical University Health Center, Biochemistry Laboratory. Written informed consents were taken from all blood donors. A small questionnaire for gathering the demographic information was also given to the volunteers.

Only Turkish subjects were included in the study, therefore study sample totally comprised of Caucasians (Turkish), without any other ethnicities (Africans or Asians). When the geographical distributions of subjects were concerned, most of the subjects were from the Central Anatolia region, and other regions; southern, northern and eastern Anatolia as well as Aegean region was also represented in the study sample. Therefore, the study sample used represented the Turkish population from all regions of the country.

DNA isolation

Four to five milliliter of blood samples from subjects were taken in EDTA-containing vacuumed tubes and stored

at −20°C until use. Blood samples were kept at 4°C while they were in active use. DNA was isolated from leukocytes manually by standard phenol: chloroform extraction method.

Genotyping analyses

The genetic polymorphisms of *CYP2E1* gene were determined by using the polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) technique. Three regions of human *CYP2E1* gene were amplified with PCR. These were *CYP2E1*5B, *6* and **7B*. The sequence of primer pairs, the PCR product sizes and restriction enzymes used for genotyping were given elsewhere (Hayashi et al. 1991; Wu et al. 1998; Yang et al. 2001). The amplified PCR products were visualized on 2.0% agarose gel for *CYP2E1*5B* and **7B* regions and on 1.5% gel for *CYP2E1*6* region.

Genotyping for *CYP2E1*5B* was done by digesting 10 µl of PCR product separately with 10 U of *Rsa*I and *Pst*I at 37°C for 18 h, and visualized on 2.5% agarose gel. *CYP2E1*6* and *7B genotypes were determined by digesting 20 µl of corresponding PCR products with 6 and 5 U of *Dra*I and *Dde*I, respectively, at 37°C for 24 h. Results of *Dra*I and *Dde*I digestions were analyzed on 1.8 and 2.5% agarose gels, respectively.

Statistical analysis

In this study, non-parametric Chi-Square Test was used to check if the calculated frequencies for *CYP2E1*5B*, *CYP2E1*6* and *CYP2E1*7B* single nucleotide polymorphisms fit to the Hardy–Weinberg equilibrium. The same test, with Yates' correction for continuity where necessary, was also used for comparison of the *CYP2E1* genotype distributions of Turkish population determined in this study with other populations.

Results

In the current study, three *CYP2E1* polymorphisms; **5B* located in 5′-flanking region, **6* located in intron 6 and **7B* located in promoter region of the gene have been investigated in a sample of 206 healthy subjects representing Turkish population.

*CYP2E1*5B* (C-1053T) polymorphism when digested with *Rsa*I produced the wild type genotype **1A/*1A* (c1/c1) and heterozygote **1A/*5B* (c1/c2). No mutated homozygote (variant) **5B/*5B* (c2/c2) was observed in the sample population (Fig. 1a, Table 1). The results were confirmed with digestion with *Pst*I, since this polymorphic site is located on the same fragment and complete linkage dis-

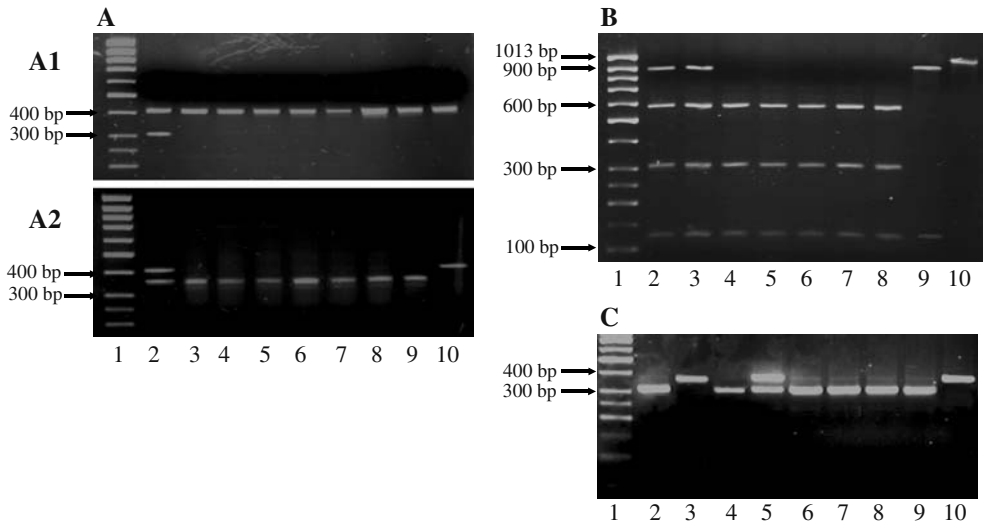

Fig. 1 Genotyping of *CYP2E1* gene for **5B, *6* and **7B* polymorphisms. **a** Detection of **5B* genotype by digestion with *Pst*I (*top panel*, A1) and *Rsa*I (*bottom panel*, A2). In Panel A1, *Lane 1*, DNA ladder; *Lanes 3–9*, homozygous wild types **1A/*1A* (c1/c1) (412 bp); *Lane 2*, heterozygote **1A/*5B* (c1/c2) (412, 294,118); *Lane 10*, undigested PCR product (412 bp). In Panel A2, *Lane 1*, DNA ladder; *Lanes 3–9*, homozygous wild type **1A/*1A* (c1/c1) (352, 60 bp); *Lane 2*, heterozygote **1A/*5B* (c1/c2) (412, 352, 60 bp), *Lane 10*, undigested PCR product (412 bp). Sample in each lane correspond to the same individuals in both gels (A1 and A2). **b** Detection of **6* genotype by digestion with *Dra*I. The amplified region in intron 6 bears two recognition sites for *Dra*I, one comprises the SNP, one does not. Upon digestion, independent of the genotype, the 997 bp PCR product yields a 121 bp band. *Lane 1*, DNA ladder; *Lanes 4–8*, homozygous wild type **1A/*1A* (T/T) (571, 305, 121 bp); *Lanes 2* and *3*, heterozygote **1A/*6* (T/A) (876, 571, 305, 121 bp); *Lane 9*, homozygous mutated **6/*6* (A/A) (876, 121 bp); *Lane 10*, undigested PCR product (997 bp). **c** Detection of **7B* genotype by digestion with *Dde*I. *Lane 1*, DNA ladder; *Lanes 2, 4, 6–9*, homozygous wild type **1A/*1A* (G/G) (302, 58 bp); *Lane 5*, heterozygote **1A/*7B* (G/T) (360, 302, 58 bp); *Lane 3*, homozygous mutated **7B/*7B* (T/T) (360 bp); *Lane 10*, undigested PCR product (360 bp)

Table 1 Genotype and allele frequencies of *CYP2E1* polymorphisms in a sample of Turkish population

CYP2E1 polymorphism	Genotype	*N*	Observed frequency % (95% CI)	Predicted freq. by Hardy–Weinberg equilibrium (%)	Allele name	*N*	Observed frequency % (95% CI)
*CYP2E1*5B* (C-1053T/G-1293C)							
Total		206				412	
Homozygous wild type	**1A*1A* (c1/c1)	198	96.12 (92.53–98.02)	96.14	**1A* (c1)	404	98.06 (96.22–99.01)
Heterozygous	**1A*5B* (c1/c2)	8	3.88 (1.98–7.47)	3.80	**5B* (c2)	8	1.94 (0.99–3.78)
Homozygous variant	**5B*5B* (c2/c2)	0	0.00 (0.00–1.83)	0.04			
*CYP2E1*6* (T7632A)							
Total		206				412	
Homozygous wild type	**1A*1A* (T/T)	173	83.98 (78.36–88.36)	84.16	**1A* (T)	378	91.75 (88.69–94.04)
Heterozygous	**1A*6* (T/A)	32	15.53 (11.22–21.10)	15.14	**6* (A)	34	8.25 (5.96–11.31)
Homozygous variant	**6*6* (A/A)	1	0.49 (0.09–2.71)	0.68			
*CYP2E1*7B* (G-71T)							
Total		206				412	
Homozygous wild type	**1A*1A* (G/G)	179	86.89 (81.60–90.83)	86.86	**1A* (G)	384	93.20 (90.35–95.25)
Heterozygous	**1A*7B* (G/T)	26	12.62 (8.76–17.85)	12.66	**7B* (T)	28	6.80 (4.75–9.65)
Homozygous variant	**7B*7B* (T/T)	1	0.49 (0.09–2.71)	0.46			

equilibrium was observed between *Rsa*I and *Pst*I positions (Watanabe et al. 1990; Hayashi et al. 1991). The genotype distribution and allele frequencies of *CYP2E1*5B* polymorphism in Turkish population is given in Table 1. In the total 206 subjects studied, 96.12% were found to be homozygous wild type **1A*/*1A (c1/c1), 3.88% were heterozygote **1A/*5B* (c1/c2) and none showed homozygote mutated variant genotype. Accordingly, the corresponding frequency for the mutated allele **5B* (c2) was 1.94% and for the wild type allele **1A* (c1) was 98.06%, as indicated in Table 1.

In case of *CYP2E1*6* (T7632A) polymorphism, digestion of corresponding PCR product with *Dra*I yielded the homozygous wild type genotype **1A/*1A* (T/T), the heterozygous genotype **1A/*6* (T/A) and the homozygous mutated variant genotype **6/*6* (A/A) as shown in Fig. 1b. The distribution of *CYP2E1*6* genotypes and allele frequencies are presented in Table 1. The genotype frequencies in 206 subjects were as follows; 83.98% homozygous wild type **1A*/*1A (T/T), 15.53% heterozygote **1A*/*6 (T/A) and 0.49% homozygous mutated variant **6/*6* (A/A). The frequency of the mutated allele **6* (A) was found to as 8.25% and of the wild type allele **1A* (T) as 91.75%, as shown in Table 1.

For the *CYP2E1*7B* (G-71T) polymorphism, *Dde*I digestion of amplified PCR product resulted in the wild type genotype **1A/*1A* (G/G), the heterozygous genotype **1A/*7B* (G/T), and the homozygous mutated genotype **7B/*7B* (T/T) (Fig. 1c). As presented in Table 1, the genotype frequencies were 86.89% for homozygous wild type **1A/*1A* (G/G), 12.62% for heterozygote **1A/*7B* (G/T), and 0.49% for homozygous mutated variant **7B/*7B* (G/G) in 206 subjects. The corresponding frequency for the mutated variant allele **7B* (T) and the wild type allele **1A* (G) was 6.80 and 93.20%, respectively (Table 1).

The expected genotype distributions calculated by the Hardy–Weinberg equation for *CYP2E1*5B, *6* and **7B* are shown in Table 1. Accordingly, all genotype frequencies were found to fit Hardy–Weinberg equilibrium.

The study comprised of 81 male and 125 female subjects, as mentioned in "Materials and methods" section. Genotype and allele frequencies for *CYP2E1*5B*, **6* and **7B* polymorphisms in male and female subjects were compared with Chi-Square test, and no significant difference were found between the two genders in terms of genotype and allele frequencies for all polymorphisms studied (data not shown).

Discussion

Owing to its particular substrate spectrum and inducibility by toxic and carcinogenic compounds, the cytochrome P450 isozyme CYP2E1 is of great interest to industrial and environmental medicine and toxicology. *CYP2E1* gene possess several polymorphisms, some of which have been associated with increased genetic susceptibility to several types of chemical-induced diseases, including several types of cancer (El Zein et al. 1997; Wu et al. 1998; Farker et al. 1998; Liu et al. 2001).

CYP2E1 polymorphism frequencies show variability in different races and ethnicities, as most other xenobiotic-metabolizing enzymes do. The genotype and allele frequencies of *CYP2E1*5B* polymorphism in the Turkish population is given in Table 1. In a total of 206 subjects studied, 96.12% were found to be homozygous wild type (**1A/*1A*), and 3.88% heterozygote (**1A/*5B*). On the other hand, no subject with homozygous mutated genotype (**5B/*5B*) was detected. Accordingly, in this study, the allele frequency of the mutated allele, *CYP2E1*5B*, was calculated to be 1.94% (Table 1). Similar to what is observed in this study, the frequency of *CYP2E1*5B* was recently reported as 1.96% in 153 Turkish subjects by Omer et al. (2001). The frequency of the mutant *CYP2E1*5B* allele is determined to be 25–36% in Eastern Asians and 2–8% in Caucasians (Kato et al. 1992; Oyama et al. 1997; Wang et al. 1999; Garte et al. 2001). As can be seen from Table 2, the allele and genotype frequencies of *CYP2E1*5B* in Turkish population were similar to Caucasian populations while they were significantly different from Chileans, Brazilians, Mexican-Americans, African-Americans and Eastern Asian populations—such as Chinese, Taiwanese and Japanese.

On the other hand, the mutated allele frequency of *CYP2E1*6* was determined as 8.25% for Turkish population (Table 1). As presented in Table 3, the genotype and allele frequencies of *CYP2E1*6* in Turkish population were significantly different from Chilean, Indian, Mexican-American, and Asian populations, but they were similar to other Caucasian populations. In agreement with the results obtained in this study, the mutated allele frequency of *CYP2E1*6* polymorphism for the control Turkish population was reported to be 8.17% by Omer et al. (2001).

So far, most of the studies on *CYP2E1* polymorphisms focused on two sites—*CYP2E1*5B* and **6* polymorphisms. On the other hand, it has been suggested that *CYP2E1*7B* (G-71T) polymorphism has functional activity during gene transcription as it is located 9 bp upstream from the consensus TATA box, and, therefore may enhance binding of transcription factor TFIID (Fairbrother et al. 1998). There have been few studies and limited data on *CYP2E1*7B* (G-71T) polymorphism frequencies and, so far, no information has been available for Turkish population. This study presented the genotype frequencies of *CYP2E1*7B* (G-71T) in the Turkish population for the first time. The genotype frequencies of *CYP2E1*7B* (G-71T) from various populations is given in Table 4. As can be seen from Table 4, the heterozygosity for the G-71T polymorphism was found to be 7.4–14.3% in the studied Caucasian populations and 12.6% in Turkish population which are also Caucasians. As far as we know, the available data concerning the allele frequency of *CYP2E1*7B* (G-71T) polymorphism is limited in the world and comprise less than 600 people (Table 4). Thus, this study with a total number of 206 Turkish subjects, would add a valuable data to the pool which could make it possible to more precisely define the population frequency of G-71T polymorphism in a healthy Caucasian population.

Table 2 Population differences in the observed genotypes for *CYP2E1*5B* (C-1053/G-1293) polymorphism

Population	*N*	*CYP2E1*5B* genotype frequency (%)			*P* value*	Reference
		**1A/*1A* (c1/c1)	**1A/*5B* (c1/c2)	**5B/*5B* (c2/c2)		
Italian	114	91.0	9.0	0.0	NS	Ingelman-Sundberg et al. (1993)
German	373	94.3	5.7	0.0	NS	Brockmöller et al. (1996)
German	297	94.9	4.4	0.7	NS	Neuhaus et al. (2004)
French	172	91.6	4.7	0.0	NS	Bouchardy et al. (2000)
Turkish	153	96.1	3.9	0.0	NS	Omer et al. (2001)
Chilean *	148	71.0	27.0	2.0	<0.0001	Quinones et al. (2001)
Brazilian*	191	90.0	9.0	1.0	0.0386	Nishimoto et al. (2000)
British Caucasoids	155	96.8	3.2	0.0	NS	Yang et al. (2001)
Indian	227	98.0	2.0	0.0	NS	Sikdar et al. (2003)
Mexican-American*	92	70.6	28.3	1.1	<0.0001	Wu et al. (1997)
African-American *	114	86.8	12.3	0.9	0.0067	Wu et al. (1997)
Chinese*	122	51.6	43.5	4.9	<0.0001	Persson et al. (1999)
Japanese*	612	63.9	32.0	4.1	<0.0001	Oyama et al. (1997)
Taiwanese*	231	58.0	35.1	6.9	<0.0001	Wang et al. (1999)
Turkish (this study)	206	96.12	3.88	0.00		

NS indicates that there is no significant difference in genotype frequencies

* *P* values express the genotype frequency comparisons between respective populations and Turkish population

Table 3 Population differences in the observed genotypes for *CYP2E1*6* (T7632A) polymorphism

Population	*N*	*CYP2E1*6* genotype frequency (%)			*P* value*	Reference
		**1A/*1A* (T/T)	**1A/*6* (T/A)	**6/*6* (A/A)		
Italian	114	83.0	17.0	0.0	NS	Ingelman-Sundberg et al. (1993)
German	373	87.3	12.4	0.3	NS	Brockmöller et al. (1996)
German	236	83.1	16.5	0.4	NS	Neuhaus et al. (2004)
French	172	87.8	11.6	0.6	NS	Bouchardy et al. (2000)
Turkish	153	84.3	15.0	0.7	NS	Omer et al. (2001)
Chilean*	129	63.6	31.0	5.4	<0.0001	Quinones et al. (2001)
British Caucasoids	155	83.2	16.1	0.7	NS	Yang et al. (2001)
Indian*	227	64.8	32.1	3.1	<0.0001	Sikdar et al. (2003)
Mexican-American*	104	72.1	24.0	3.9	0.0125	Konishi et al. (2003)
Chinese*	122	48.4	46.7	4.9	<0.0001	Persson et al. (1999)
Japanese*	76	56.6	28.9	14.5	<0.0001	Uematsu et al. (1994)
Taiwanese*	231	53.7	37.7	8.6	<0.0001	Wang et al. (1999)
Turkish (this study)	206	83.98	15.53	0.49		

* *P* values express the genotype frequency comparisons between respective populations and Turkish population

NS indicates that there is no significant difference in genotype frequencies

Table 4 Population differences in the observed genotypes for *CYP2E1*7B* (G-71T) polymorphism

Population	*N*	*CYP2E1*7B* genotype frequency (%)			*P* value*	Reference
		**1A/*1A* (G/G)	**1A/*7B* (G/T)	**7B/*7B* (T/T)		
Northern European[a]	115	89.6	10.4	0.0	NS	Fairbrother et al. (1998)
British Caucasoids	155	90.3	9.0	0.7	NS	Yang et al. (2001)
German[a]	56	85.7	14.3	0.0	NS	Thier et al. (2002)
German	299	92.6	7.4	0.0	NS	Neuhaus et al. (2004)
Swedish[a]	37	91.9	8.11	0.0	NS	Ernstgard et al. (2004)
Turkish (this study)	206	86.89	12.62	0.49		

NS indicates that there is no significant difference in genotype frequencies

* *P* values express the genotype frequency comparisons between respective populations and Turkish population

[a] The frequencies are calculated according to the data presented in the corresponding articles

In view of significant inter-ethnic differences of *CYP2E1* polymorphisms, it was an important issue to establish its genotype distribution and allele frequencies in Turkish population. Such studies on control populations would contribute to the attempts to more precisely define population-frequencies of polymorphisms in control populations. Population studies like this could be useful in assessing the susceptibility of different populations to diseases related to *CYP2E1* polymorphisms and in determining whether it is necessary to design different therapeutic and toxicological protocols to reduce the risk of population.

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