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ORIGINAL ARTICLE

Genotype and Allele Frequency of *CYP3A4 -392A>G* in Turkish Patients with Major Depressive Disorder

Majör Depresif Bozukluğu Olan Türk Hastalarında *CYP3A4 -392A>G* Genotip ve Allel Frekansı

Zuhal UÇKUN[1], Bora BASKAK[2], Hatice ÖZDEMİR[3], Erguvan Tuğba ÖZEL-KIZIL[2], Halise DEVRİMCİ-ÖZGÜVEN[2], Halit Sinan SÜZEN[4]*

[1]Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Mersin, Turkey
[2]Ankara University, Faculty of Medicine, Department of Psychiatry, Ankara, Turkey
[3]Kırıkkale University, Faculty of Medicine, Department of Psychiatry, Kırıkkale, Turkey
[4]Ankara University, Faculty of Pharmacy, Department of Toxicology, Ankara, Turkey

ABSTRACT

Objectives: Genetic polymorphisms may help for individualized drug dosing and improved therapeutics. CYP3A4 is responsible for the metabolism of more than 50% of the commonly used drugs and metabolizes typical antipsychotic medications and antidepressant drugs. The objective of the study was to assess the genotype and allele frequencies of *CYP3A4 -392A>G* in Turkish patients with major depressive disorder receiving any SSRIs and to compare these results with the frequencies of other ethnic groups.

Materials and Methods: Genotyping analyses of *CYP3A4 -392A>G* was conducted on 84 Turkish patients using the PCR-RFLP technique.

Results: The allele frequencies were found as 0.982 (A) and 0.018 (G) for *CYP3A4 -392A>G*. The genotype frequencies were determined as 0.976 (AA), 0.012 (AG), and 0.012 (GG). The genotype frequencies were consistent with the Hardy-Weinberg equilibrium.

Conclusion: The genotype and allele frequencies of *CYP3A4 -392A>G* were determined to be low in Turkish patients with major depressive disorder receiving SSRIs. Furthermore, the results of the study were compared with those of other ethnic groups and they displayed pronounced differences among other ethnic groups, especially black subjects.

Key words: *CYP3A4 -392A>G*, polymorphism, Turkish patients, major depressive disorder

ÖZ

Amaç: Genetik polimorfizmler, bireyselleştirilmiş ilaç dozlaması ve geliştirilmiş terapötikler için yardımcı olabilir. CYP3A4 yaygın olarak kullanılan ilaçların %50'sinden fazlasının metabolizmasından sorumludur ve tipik olarak antipsikotik ilaçlar, antidepresan ilaçları metabolize eder. Bu çalışmanın amacı, herhangi bir SSGİ alan majör depresif bozukluğu olan Türk hastalarında *CYP3A4 -392A>G*'nin genotip ve alel frekanslarını değerlendirmek ve sonuçlarımızı diğer etnik gruplardaki frekanslarla karşılaştırmaktır.

Gereç ve Yöntemler: *CYP3A4 -392A>G*'nin genotiplendirme analizi, 84 Türk hastasında PZR-RFLP tekniği ile gerçekleştirilmiştir.

Bulgular: *CYP3A4 -392A>G* için allel frekanslarının 0.982 (A) ve 0.018 (G) olduğu saptanmıştır. Genotip frekanslarının ise 0.976 (AA), 0.012 (AG) ve 0.012 (GG) olduğu tespit edilmiştir. Genotip frekansları Hardy-Weinberg dengesiyle uyumludur.

Sonuç: *CYP3A4 -392A>G*'nin düşük frekansı, *CYP3A4* ilaç metabolize edici enzimin SSGİ'ler üzerinde oldukça düşük bir etkisinin olacağı önerilmektedir. Bunun yanı sıra, araştırmanın sonuçları diğer etnik gruplarla karşılaştırılmış olup etnik grup farklılıklarının özellikle de siyah deneklerde belirlenmiştir.

Anahtar kelimeler: *CYP3A4 -392A>G*, polimorfizm, Türk hastalar, majör depresif bozukluk

*Correspondence: **E-mail:** suzen@.ankara.edu.tr, **Phone:** +90 533 345 37 99 **ORCID-ID:** orcid.org/0000-00003-1779-5850
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INTRODUCTION

Cytochrome P450 (CYP) is the major metabolizing enzymatic system in humans and CYP enzymes are responsible for the metabolism of exogenous compounds, including most clinically used drugs, mutagens, carcinogens,[1,2] and some endogenous compounds, such as prostaglandins, steroids, vitamins, fatty acid derivatives and retinoic acid derivatives, and thromboxanes.[2,3] CYP enzymes are responsible for the biotransformation of lipophilic compounds to polar metabolites, which can be excreted by the urine or bile. There are three major CYP families that encode enzymes that play an important role in phase I metabolism: CYP1, CYP2, and CYP3.[3] The CYP3A subfamily is the most abundant CYP enzyme and represents about 30% of the total CYP in the human liver.[2] Approximately 65% of current drugs used are metabolized by CYP enzymes and 45-60% of clinically administered drugs, and exogenous and endogenous compounds such as streoids, are metabolized by the CYP3A subfamily.[4,5] The CYP3A subfamily consists of 4 members: *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*.[5] The *CYP3A4* enzyme is the most abundant CYP isoform in the liver and intestine, representing 60% and 70% of the total P450 amount, respectively. *CYP3A4* is responsible for the metabolism of more than 50% of commonly prescribed drugs and metabolizes typical antipsychotic medications, antidepressant drugs (Table 1).[6] Its interindividual hepatic expression varies 60-fold, resulting in therapeutic failure, unpredictable adverse effects or severe drug toxicity.[7]

The *CYP3A4* gene is located on chromosome 7q21.3-q22.1, is 27,592 base pairs (bp) long, and has 13 exons.[3,8] Genetic polymorphisms of *CYP3A4* were unknown until 1996.[8] However, nowadays, *CYP3A4* is known to be polymorphic, and more than 30 single nucleotide polymorphisms have been described in the *CYP3A4* gene. The most common single-nucleotide polymorphism *-392A>G* in the promoter region of the *CYP3A4* gene has been described. *CYP3A4 -392A>G* (rs2740574) is also known as *CYP3A4*1B*. It is known that the *CYP3A4*1B* polymorphism alters the transcription efficiency of the gene and hence the overall activity of *CYP3A4*.[9]

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for mild-to-severe major depressive disorder (MDD).[10] The objective of this study was to assess the genotypic and allelic frequencies of the *CYP3A4*1B* in Turkish patients with MDD receiving SSRIs and to compare the results with frequencies in other ethnic groups.

MATERIALS AND METHODS

Subjects

The study was conducted on 84 Turkish patients with MDD at the Departments of Psychiatry, Schools of Medicine, Ankara University and Kırıkkale University, Turkey. All participants were administered with SSRIs. Approval for this study was obtained from the Ethics Committee of the Ankara University (21 April 2008, protocol no: 128-3581). The study was conducted in accordance with Good Clinical Practices and the Helsinki Declaration. All subjects gave their written informed consent to participate in this study. The demographic data of the patients with MDD are shown in Table 2.

Blood sampling

Blood samples (10 mL) were collected in vacutainer tubes containing EDTA as an anticoagulant between 08:00 and 09:00 a.m. at the 4th and/or 6th weeks of treatment. The Wizard Genomic DNA Purification Kit (Promega) was used to isolate genomic DNA from the cell fraction. DNA yields were determined by measuring the absorbance at 260 nm (A_{260}). All samples were stored at -80˚C until analysis.

Genotyping

The *CYP3A4*1B* (rs 2740574; *-392A>G*) polymorphism was identified using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method of Cavalli et al.[11] with minor modifications. The primers employed were F: 5'-GGAATGAGGACAGCCATAGAGACAAGGGGA-3', R: 5'CCTTTCAGCTCTGTGT TGCTCTTTGCTG-3'. PCR was performed in a 25-µL reaction mixture containig 300-500 ng of genomic DNA, 10 pmol of each primer, 0.2 mM each deoxynucleotidetriphosphate, 10 x PCR buffer, 1.5 mM $MgCl_2$, and 1.25 unit of Taq polymerase (Fermentase) on the MBS Satellite Thermal Cycler (Thermo, UK). After initial denaturation for 5 min at 97˚C, PCR was performed for 30 cycles of 60 s at 95˚C, 90 s at 60˚C, 60 s at 72˚C, and with a final step of 72˚C for 10 min for elongation. No added DNA (negative control) reactions were included in each PCR analysis to ensure that the agents

Table 1. Common drugs metabolized by *CYP3A4*[6]

Group of drugs	Drug name
Antidepressants (SSRIs; SNRIs; tricyclics; others)	Citalopram, escitalopram, paroxetine, fluoxetine; venalafaxine, trazodone; amitriptyline, imipramine, clomipramine; buspirone nefazodone, mirtazapine
Antipsychotics (first generations; second generations)	Haloperidol, perphenazine; aripiprazole, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, diazepam, medazolam, temazepam, lorazepam, clonazepam
Opiates	Codeine, methadone, fentanyl, buprenorphine
Hypnotics	Zopiclone, zaleplon, zolpidem
Antibiotics	Erythromycin, clarithromycin, telithromycin
Phosphodiesters inhibitors	Sildenafil, tadalafil

contained no contaminating DNA. The PCR product (385 bp) was analyzed electrophoretically on a 2% agarose gel stained with ethidium bromide (500 ng/mL). Ten microliters of the PCR product were digested at 37˚C overnight with 10 U of *MboII* with the appropriate buffer in a total volume of 20 µL. As shown in Figure 1, the digestion resulted in fragments of 175, 169, and 41 bp for the AA (wild type), and fragments of 210 and 175 bp for the GG (mutant). The digested fragments were electrophoresed on a 2% agarose gel and visualized using ethidium bromide.

Table 2. Baseline characteristics of the patients with major depressive disorder

Demographic and genotypic characteristics	Mean ± SD	Range (min-max)
Body weight (kg)	70.12±14.39	45.5-105
BMI (kg/m^2)	25.94±5.14	16.1-41.14
	n	%
Sex		
Female	68	81
Male	16	19
Age range		
≤40	53	**63**
>40	31	**37**
***CYP3A4* genotypes**		
Genotypic frequencies		
AA (or **1A*1A)*	82	97.6
AG (or **1A*1B)*	1	1.2
GG (or **1B*1B)*	1	1.2
Allelic frequencies		
A (or **1A*)	165	98.6
G (or **1B*)	3	1.8

BMI: Body mass index

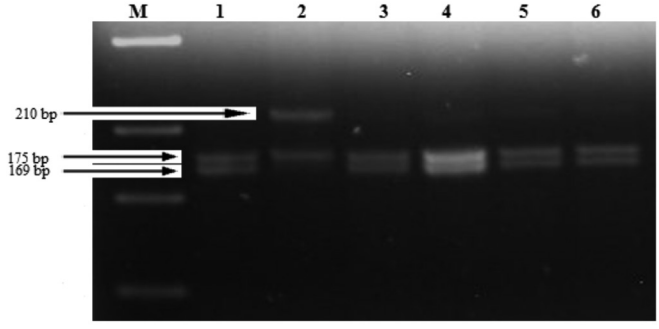

Figure 1. RFLP for the CYP3A4*1B polymorphism. Lane M: Marker, Lane 2: mutant (210, 175 bp), Lane 1,3-6: wild type (175, 169, 41 bp)

Statistical analysis

Genotype counting was used to calculate the allele and genotype frequencies. The observed and expected genotype frequencies of *CYP3A4* were compared using the Hardy-Weinberg equilibrium. The comparison of the allele frequencies in the present investigation with those in other populations was made using the chi-square test. *P* values <0.05 and <0.001 were considered statistically significant.

RESULTS

*CYP3A4*1B* (-392A>G) polymorphism analysis was conducted on 84 Turkish patients with MDD. Of the 84 patients, 68 (81% of patients) were female, whereas 16 (19% of them) were male (*p>0.05*) (Table 2). The body weight of the patients varied from 45.5 to 105 kg, with a mean of 70.12±14.39 kg. The body mass index (of the patients) ranged from 16.1 to 41.14 kg/m^2, with a mean of 25.94±5.14 kg/m^2. In the study, 53 subjects (63%) were aged ≤40 years, and 31 subjects (37%) were aged >40 years.

The frequencies of the *AA*, *AG*, and *GG* genotypes were 0.976, 0.012, and 0.012, respectively. According to these results, the frequencies of *A* and *G* alleles were 0.982 and 0.018, respectively (Table 2). These results were consistent with the expected genotype frequencies of the Hardy-Weinberg equilibrium (*p>0.05*).

DISCUSSION

Factors that can influence the response of a patient to any given drug depend on intrinsic (e.g., genetic and non-genetic factors such as sex, age, organ dysfunctions, disease state, and race/ethnicity) and extrinsic factors (e.g., use of alcohol, smoking, diet, and concomitant medication).[12,13] Genetics is estimated to account for 20 to 95% of variability in drug effects and disposition.[14] It has been shown that much of this variability is produced by genetic polymorphisms of the CYP enzymes.[4] CYP enzymes perform extensive structural differences because of genetic polymorphisms in the corresponding genes, and thus causing different enzymatic activities and giving rise to great intra- and inter-population variation in drug efficacy and adverse reactions.[15]

Approximately 65% of drugs in current use are metabolized by CYP enzymes, and 45-60% of clinically administered drugs, exogenous and endogenous compounds such as streoids, are metabolized by the *CYP3A* subfamily.[4,5] *CYP3A4* is a polymorphic enzyme, and its interindividual hepatic expression varies 60-fold.[7] *CYP3A4*1B*, described as the most common variant, has been speculated to have reduced activity.[16] Significant differences in allele frequencies of *CYP3A* variant occur among ethnic groups.[16] Polymorphisms in human xenobiotic metabolizing genes show parallelism in ethnic, racial, and geographic distribution, and the ethnic-specific impact on CYP genes is known.[9]

In this study, we aimed to investigate the *CYP3A4*1B* allele frequencies in Turkish patients with MDD receiving SSRIs and to compare the results with the frequencies of other ethnic groups. The allele frequencies in the Turkish population were

Table 3. Allele frequencies of *CYP3A4*1B* in different ethnic populations

		CYP3A4 allele frequencies			
Population	**Healthy and control populations**	**n**	****1A***	****1B***	**References**
White					
Turkish	Healthy	186	0.986	0.014	Sayitoglu et al.[16]
Turkish	Major depressive disorder	84	0.982	0.018	The present study
Turkish	Familial Mediterranean fever patients	46	0.967	0.033	Dogruer et al.[17]
Turkish	Children with lower urinary tract symptoms	34	0.956	0.044	Gurocak et al.[18]
Turkish	Healthy children	42	0.939	0.061	Gurocak et al. [18]
Caucasian (Germany)	Hospital controls	428	0.972	0.028	Dally et al.[20]
Australian	Control for ovarian cancer	276	0.969	0.031	Spurdle et al.[21]
Australia	Control for breast cancer	500	0.967	0.033	Spurdle et al. [21]
European	Healthy	93	0.962	0.038	Garsa et al.[22]
Caucasian American (Southern California)	Healthy	117	0.961	0.039	Paris et al. [23]
Finnish	Healthy	118	0.958	0.042	Sata et al.[24]
Spanish	Healthy	163	0.957	0.043	Gervasini et al.[25]
Portuguese	Control	337	0.951	0.049	Nogal et al.[3]
Dutch Caucasian	Healthy	199	0.947	0.053	van Schaik et al.[26]
Scottish	Healthy	101	0.946	0.054	Tayeb et al.[27]
Caucasian American* (Philadelphia)	Controls	340	0.921	0.079	Zeigler-Johnson et al.[28]
Saudi*	Healthy	101	0.910	0.090	Tayeb et al.[27]
Caucasian American* (Philadelphia)	Healthy	94	0.904	0.096	Rebbeck et al.[29]
European-Brazilians*	Healthy	91	0.901	0.099	Kohlrausch et al.[30]
Hispanic*	Controls	121	0.893	0.107	Paris et al.[23]
Asians					
Taiwanese	-	130	1.000	0.000	Walker et al.[31]
Japanese	Healthy	128	1.000	0.000	Ando et al.[32]
Japanese	Healthy	77	1.000	0.000	Ball et al.[33]
Japanese	Hospital patients	416	1.000	0.000	Fukushima-Uesaka et al.[34]
Chinese	Healthy	78	1.000	0.000	Ball et al.[33]
Chinese	Healthy	118	1.000	0.000	Sata et al.[24]
Vietnamese	Healthy	78	0.979	0.021	Veiga et al.[35]
Jordanian	Healthy	173	0.965	0.035	Yousef et al.[36]
Black**					
African-Brazilians	Healthy	86	0.616	0.384	Kohlrausch et al.[30]
African	Controls	67	0.560	0.440	McDaniel et al.[37]
African American	-	70	0.470	0.530	Walker et al.[31]

Table 3. Continue					
African American	Healthy	116	0.457	0.543	Paris et al.[23]
African American	Healthy	186	0.454	0.546	Ball et al.[33]
African American	Controls	103	0.427	0.573	Bangsi et al.[38]
African American	Controls	130	0.408	0.592	Zeigler-Johnson et al.[28]
African	Healthy	150	0.333	0.667	Sata et al.[24]
Ghanaian	Healthy	100	0.310	0.690	Tayeb et al.[27]
African American	Healthy	15	0.200	0.800	Wandel et al.[39]
Ghanaian	Controls	118	0.195	0.805	Zeigler-Johnson et al.[28]
African	Healthy	88	0.176	0.824	Garsa et al.[22]

Differences in allele frequencies were assessed by χ^2 test. n total number of subjects. Significant at *p<0.05 and **p<0.001 when compared with the present study

0.982 and 0.018 for **1A* and **1B* alleles, respectively (Table 3). A comparison of the results of this investigation with the results of the other studies is presented in Table 3. Sayitoglu et al.[16] reported that **1B* allele frequency was 0.014 in healthy Turkish subjects. Dogruer et al.[17] reported that **1B* allele frequency was 0.033 in Turkish patients with familial Mediterranean fever. Gurocak et al.[18] also reported that **1B* allele frequency was 0.044 and 0.061 for Turkish children with lower urinary tract symptoms and healthy Turkish children, respectively. The allele frequencies of these studies were not significantly different from the results of this study (*p>0.05*). However, when compared with black subjects, the allele frequency of Turkish subjects showed marked differences. The **1B* variant allele frequencies were identified more frequently in African-American, African Brazilians, African, and Ghanaian individuals when compared with Turkish subjects (*p<0.001*). Furthermore, **1B* variant allele frequencies were also reported to be higher in Caucasian American (Philadelphia), Saudi, European-Brazilians, Hispanic populations when compared with Turkish populations (*p<0.05*). The distribution of **1A* and **1B* alleles in Turkish populations was similar to those reported for Caucasians (Germany), Australian, European, Finnish, Spanish, Portuguese, Caucasians American (Southern California), Ducth Caucasian, and Scottish populations (Table 3).

The allelic frequency of *CYP3A4*1B* changes among different ethnic groups; *CYP3A4*1B* allelic frequency is dominant in black subjects with a range of 38.4 to 82.4% (Table 3). On the other hand, this polymorphism is very rare in Asian ethnic groups, including Vietnamese and Jordanian groups, ranging from 0 to 9.0%. This polymorphism is absent in East Asian populations including the Japanese, Chinese, and Taiwanese, and present in White ethnic groups with a range of 1.8 to 14.3%. Consequently, it seems that the *CYP3A4*1B* polymorphism is more frequent in White ethnic groups than in East Asian populations, and is more common in black subjects than in White ethnic groups. There is a minimal clinical effect of the *CYP3A4*1B* polymorphism on Asian ethnic groups. However, the *CYP3A4*1B* polymorphism seems to be more clinically important in black subjects.

CONCLUSION

The study introduces evidence of a low frequency of *CYP3A4*1B* allele in Turkish patients and compared this frequency with those of other ethnic groups. Given the effect of *CYP3A4* on the efficacy of drugs, the genetic backgrounds of individuals and populations are accepted as a significant factor to be considered in the recipe of individualized medicine.[19] Determining the expression of *CYP3A4* may detect drug safety and efficacy and therefore help people to use the right dose of drugs.[15] *CYP3A4*1B* should be taken into consideration in populations where the allele frequency is high. On the other hand, a larger sample size would be needed to determine the *CYP3A4*1B* polymorphism in populations where the allele frequency is low.

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