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

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

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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 terapotikler için yardımcı olabilir. CYP3A4 yaygın olarak kullanılan ilaçların %50’sinden fazlasının metabolizmasından sorumlu 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 sonuçlarının diğer etnik gruplardaki frekanslarıyla karşılaştırılmaktır.

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 uyumlu bulundu.

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

Anahtar kelimeler: CYP3A4 -392A>G, polimorfizm, Türk hastaları, majör depresif bozukluk
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, and some endogenous compounds, such as prostaglandins, steroids, vitamins, fatty acid derivatives and retinoic acid derivatives, and thromboxanes. 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. The CYP3A subfamily is the most abundant CYP enzyme and represents about 30% of the total CYP in the human liver. 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 steroids, are metabolized by the CYP3A subfamily. The CYP3A subfamily consists of 4 members: CYP3A4, CYP3A5, CYP3A7, and CYP3A43. 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). Its interindividual hepatic expression varies 60-fold, resulting in therapeutic failure, unpredictable adverse effects or severe drug toxicity.

The CYP3A4 gene is located on chromosome 7q21.3-q22.1, is 27,592 base pairs (bp) long, and has 13 exons. Genetic polymorphisms of CYP3A4 were unknown until 1996. 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.

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for mild-to-severe major depressive disorder (MDD). 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 Kirikkale 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 (A260). 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. with minor modifications. The primers employed were F: 5'GGGACGTGCAAAGACGACCCATAGAGCAAGCGAGA3'; R: 5'CCTTTCAGCTCTGTGT TGCTCTTTGCTG-3'. PCR was performed in a 25-μL reaction mixture containing 300-500 ng of genomic DNA, 10 pmol of each primer, 0.2 mM each dNTPs, 1 x PCR buffer, 1.5 mM MgCl2, and 1.25 units 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<sup>4</sup> |
|-------------------------------|----------------------------------|
| **Group of drugs**             | **Drug name**                     |
| Antidepressants (SSRIs; SNRIs; tricyclics; others) | Citalopram, escitalopram, paroxetine, fluoxetine; venlafaxine, 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 |
| Phosphodiester 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.

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/m², with a mean of 25.94±5.14 kg/m². 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). Genetics is estimated to account for 20 to 95% of variability in drug effects and disposition. It has been shown that much of this variability is produced by genetic polymorphisms of the CYP enzymes. 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. 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 steroids, are metabolized by the CYP3A subfamily. CYP3A4 is a polymorphic enzyme, and its interindividual hepatic expression varies 60-fold. CYP3A4*1B, described as the most common variant, has been speculated to have reduced activity. Significant differences in allele frequencies of CYP3A variant occur among ethnic groups. Polymorphisms in human xenobiotic metabolizing genes show parallelism in ethnic, racial, and geographic distribution, and the ethnic-specific impact on CYP genes is known.

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 consistent with the expected genotype frequencies of the Hardy-Weinberg equilibrium (p>0.05).

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/m²)                               | 25.94±5.14 | 16.1-41.14     |
| Sex                                       |           |                |
| Female                                    | 68        | 81             |
| Male                                      | 16        | 19             |
| Age range                                 |           |                |
| ≤40                                       | 53        | 63             |
| >40                                       | 31        | 37             |
| 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)
Table 3. Allele frequencies of CYP3A4*1B in different ethnic populations

| 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      |                                 | 46    | 0.967 | 0.033 | Dogruer et al. 17      |
| patients                                   |                                 |       |       |       |                       |
| Turkish Children with lower urinary tract |                                 | 34    | 0.956 | 0.044 | Gurocak et al. 18      |
| symptoms                                   |                                 |       |       |       |                       |
| 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**                              |                                 |       |       |       |                       |
| Turkish 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                           | Healthy                        | 118   | 0.958 | 0.042 | Sata et al. 24         |
| Spanish Healthy                           | Healthy                        | 163   | 0.957 | 0.043 | Gervasini et al. 25    |
| Portuguese Control                        | 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                          | 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                            | 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              | Controls                       | 91    | 0.901 | 0.099 | Kohlrausch et al. 20   |
| Hispanic* Controls                        |                                 | 121   | 0.893 | 0.107 | Paris et al. 23        |
| **Asians**                                |                                 |       |       |       |                       |
| Taiwanese -                               | 130                             | 1.000 | 0.000 |       | Walker et al. 31       |
| Japanese Healthy                          | Healthy                        | 128   | 1.000 | 0.000 | Ando et al. 32         |
| Japanese Healthy                          | Healthy                        | 77    | 1.000 | 0.000 | Ball et al. 33         |
| Japanese Hospital patients                | 416                             | 1.000 | 0.000 |       | Fukushima-Uesaka et al. 24 |
| Chinese Healthy                           | Healthy                        | 78    | 1.000 | 0.000 | Ball et al. 33         |
| Chinese Healthy                           | Healthy                        | 118   | 1.000 | 0.000 | Sata et al. 24         |
| Vietnamese Healthy                        | Healthy                        | 78    | 0.979 | 0.021 | Veiga et al. 35        |
| Jordanian Healthy                         | Healthy                        | 173   | 0.965 | 0.035 | Yousef et al. 26       |
| **Black**                                 |                                 |       |       |       |                       |
| African-Brazilians Healthy                | Healthy                        | 86    | 0.616 | 0.384 | Kohlrausch et al. 30   |
| Asian                                      | Controls                       | 67    | 0.560 | 0.440 | McDaniel et al. 37     |
| African American                          | -                              | 70    | 0.470 | 0.530 | Walker et al. 31       |
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.\textsuperscript{36} reported that *1B allele frequency was 0.014 in healthy Turkish subjects. Dogruer et al.\textsuperscript{37} reported that *1B allele frequency was 0.033 in Turkish patients with familial Mediterranean fever. Guracak et al.\textsuperscript{38} 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), Ducht 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.

Table 3. Continue

|                | Healthy | Controls | Healthy | Controls | Healthy | Controls |
|----------------|---------|----------|---------|----------|---------|----------|
| African American |         |          | 116     | 0.457    | 0.543   |          |
| African American | Healthy |          | 186     | 0.454    | 0.546   |          |
| African American | Controls |          | 103     | 0.427    | 0.573   |          |
| African American | Controls |          | 130     | 0.408    | 0.592   |          |
| African         | Healthy |          | 150     | 0.333    | 0.667   |          |
| Ghanaian        | Healthy |          | 100     | 0.310    | 0.690   |          |
| Ghanaian        | Controls |          | 118     | 0.195    | 0.805   |          |
| African         | Healthy |          | 88      | 0.176    | 0.824   |          |

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

### 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.\textsuperscript{19} Determining the expression of CYP3A4 may detect drug safety and efficacy and therefore help people to use the right dose of drugs.\textsuperscript{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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### Conflict of Interest

No conflict of interest was declared by the authors.

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