Polymorphism

RESEARCH

# Preliminary study of CYP3A4*18 and CYP3A5*3 single nucleotide polymorphisms in an Azerbaijani population

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## ABSTRACT

**Aim**: The human cytochrome CYP3A isoenzymes collectively cover the largest portion of the liver CYP proteins, where they play crucial roles in the metabolism of 45-60% of all drugs. Among the SNPs of CYP3A isoforms, *CYP3A4*18* and *CYP3A5*3* variants are the most common allelic variations, which may affect the activity of theseenzymes. The aim of this study is identification of the frequency of *CYP3A4*18* and *CYP3A5*3* polymorphisms in an Azerbaijani population.

**Methods**: We identified *CYP3A4*18* and *CYP3A5*3* allele and genotype frequencies in 100 Azerbaijani individuals by using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) technique. The results were confirmed by next-generation and Sanger sequencing.

**Results**: The *CYP3A5*3*/3** allele frequency was 97.5% (95 out of 100), with the **1* allele frequency being 2.5% (5 out of 100). All the volunteers (100/100) were wildtype for the *CYP3A4*18* allele.

**Conclusion**: In conclusion, this small-scale study suggests that 95% of Azerbaijani individuals with *CYP3A5*3/*3* genotype might fail to express CYP3A5 protein. Therefore, our results highlight the importance of genotyping of *CYP3A5*3* and *CYP3A4*18* polymorphisms as well as demonstrate a demand for further investigations to evaluate their clinical relevance in a larger sample size.

KEYWORDS: CYP3A4; CYP3A5; PCR-RFLP; Cytochrome P450; Azerbaijani

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## INTRODUCTION

The $P_{450}$ superfamily catalyzes the metabolism of a large number of structurally diverse endogenous and exogenous molecules. In the human genome, there are 57 genes encoded by 18 mammalian cytochrome P450 (CYP) families that are classified only on the basis of amino-acid sequence homology (Nebert et al., 2013). The process of gene duplication and gene conversion caused the genesis of CYP families (Kuehl et al., 2001). Cytochromes P450 can be functionally divided into two main classes: the first group includes biosynthesis of fatty acids, steroids, and bile acids, whereas the second class involves xenobiotics metabolism primarily carried out by CYP 1, CYP 2, and CYP 3 families (Balram et al., 2003).

The human cytochrome P450 3A (CYP3A) is the most highly expressed subfamily in the human liver and small intestine (Cholerton et al., 1992). CYP3A isoenzymes (CYP3A4, CYP3A5, CYP3A7, and CYP3A43) collectively cover the largest portion of the liver CYP protein, where they play a crucial role in the metabolism of almost 60% of all drugs and metabolize several other compounds, including carcinogens, toxins, and hormones (Hustert et al., 2001, Alessandrini et al., 2011)). Moreover, the isoforms mentioned above catalyze the oxidative, peroxidative, and reductive metabolism of endobiotics and procarcinogenic structures (Kuehl et al., 2001).

The activity of CYP3A enzymes dramatically varies from individual to individual and affects the efficacy and safety of drugs substrated by CYP3A (Fukuen et al., 2002). For instance, variation in cytochrome P450 3A expression is essential for narrow therapeutic indices (chemotherapeutics and immunosuppressants) as such alteration in CYP3A can cause clinically significant differences in drug toxicity response. Besides, as CYP3A participates in the metabolism of estrogens associated with estrogen-mediated carcinogenicity; thus, modification in the mentioned family can affect the circulating levels of these hormones and risk of breast cancer (Kuehl et al., 2001).

Among the CYP3A family, CYP3A4 is the most abundant drug-metabolizing enzyme in the adult liver, composing nearly 15-20% of hepatic CYP content and is a major enzyme present in small intestinal enterocytes (Sciencedirect.com, 2007). CYP3A5 is known to be the second most crucial CYP3A liver protein and is expressed at 20-fold lower levels than CYP3A4 in individuals who express this CYP isoform. Nonexpression of CYP3A5 is commonly caused by genetic polymorphisms that produce aberrant splicing and truncated protein (Kuehl et al., 2001).

Recent studies report a number of functional polymorphisms of CYP3A4 and CYPA5 families. However, among the SNPs, *CYP3A4*18* variant located in the exon 10 is known as the most common allelic variation of CYP3A4. This alteration involves nucleotide change from thymine (T) to cytosine (C) transition at position 878 and causes an amino acid change from leucine to proline at codon 293 (Leu293Pro). Interestingly, *CYP3A4*18* variant was revealed to be associated with a high turnover of testosterone and chlorpyrifos compared to wildtype (Dai et al., 2001).

Another prevalent allelic variant is *CYP3A5*3*. It is located in the intron 3 of CYP3A5 and creates a cryptic consensus splice site (Liu et al., 2002). The mentioned alteration causes production of mRNA encoding a protein, with decreased enzymatic activity or complete inactivation of the enzymes. (Emich-Widera et al., 2010). Thus, this SNP may play a significant role in the metabolic profile of many drugs.

In this study, we identified the frequency of both *CYP3A4*18* and *CYP3A5*3* in an Azerbaijani population as the determination of the frequency of the variants would be helpful in further pharmacogenetics research.

# METHODS

## Subjects and DNA extraction

This study was approved by the ethics committee of the Institute of Hematology and Transfusiology (IHT), named after B. Eyvazov, which complies with the Declaration of Helsinki of 1964, as revised in 2013. The protocol of written informed consent was obtained from all the patients involved in the investigation. Patients were recruited from the Institute of Hematology and Transfusiology, named after B. Eyvazov.

Our experiment involved a group of 100 unrelated subjects (32 males and 68 females) aged 15-81 years (mean: 36; standard deviation: 16), randomly selected from different areas of Azerbaijan.

The study includes individuals who have been admitted to IHT between the date of February 2017 and December 2019, belong to the Azerbaijani ethnic group and have resided in Azerbaijan for three consecutive generations. Due to established inclusion criteria, we did not include subjects with a history or evidence of hepatic or hematological abnormalities, hepatitis B or C or HIV infection, or any other acute or chronic disorders.

Whole blood samples (2ml) were collected in vacutainer tubes containing ethylene diamine tetraacetic acid (EDTA). Genomic DNA isolation was performed using a DNA extraction kit, QIAGEN QIAamp DNA Blood Mini kit (QIAGEN, Hilden, Germany), according to the manufacturer's instructions. Genotyping was conducted at the Institute of Genetic Resources of Azerbaijan National Academy of Sciences (ANAS). DNA quality and quantity were measured by NanoDrop *2000c* Spectrophotometers (Thermo Scientific).

## Genotyping of CYP3A4*18 polymorphism

The amplification of *CYP3A4*18* was carried out by using forward 5'CACATCAGAATGAAACCACC-3' and reverse 5'-AGAGCCTTCCTACATAGAGTCA-3' primers in 25-µl tubes of 2.5 µl of 10x PCR buffer, 2.0 µl $MgCl_2$, 0.25 µl dNTPs, 0.25 FIREPOL Taq Polymerase, 0.5 µl of each primer, 18 µl deionized water and 1 µl DNA. The program was set to initial denaturation at 95 °C for 5 minutes, followed by 35 cycles at 95°C for 30s, 51°C for 1 minute, 72°C for 2 minutes, and a final extension step at 72°C for 5 min. Gel electrophoresis of 450-bp PCR products was performed on a 1.5% agarose gel at 120 V for 45 minutes.

2.5 µl of PCR products were digested with 0.5 units of restriction enzyme Msp1 (New England BioLabs, BioLabs) for an hour at 37°C, and the genotyping was done on a 3% agarose gel. Only the homozygous wildtype (TT) allele was revealed by the presence of undigested 450bp (Figure 1a).

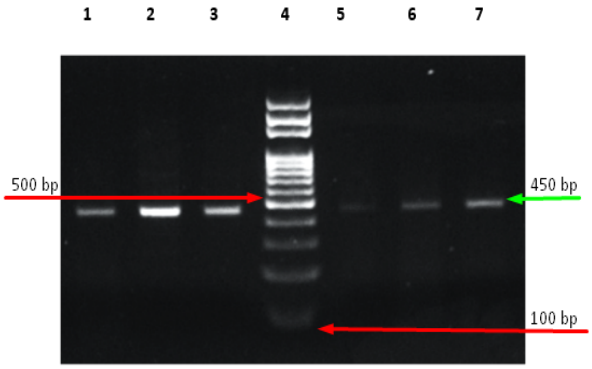


Figure 1(a). Gel electrophoresis for *CYP3A4*18 (digestion enzyme MspI)* and *CYP3A5*3 (digestion enzyme SspI)*. Lane 4 includes a 100-bp ladder. All the lanes reveal a homozygous wild-type genotype (*TT*).

## Genotyping of CYP3A5*3 polymorphism

*CYP3A5*3* (G6986A) single nucleotide polymorphism was identified using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. A PCR assay using forward primer pair 5'-GGTCCAAACAGGGAAGAAATA-3' and reverse primer 5'-CATGACTTAGTAGACAGATGAC-3' was performed in 25-µl PCR tubes, and the mixture composed of 2.5 µl of 10x PCR buffer, 2.0 µl magnesium chloride ($MgCl_2$), 0.25 µl dNTPs, 0.25 FIREPOL Taq Polymerase (Solis Biodyne, Estonia),

0.5 µl of each primer, 17 µl deionized water and 2 µl DNA. The process starts with an initial denaturation step of 95°C for 5 minutes, followed by 35 cycles at 95°C for 30s, 50°C for 1 minute, 72°C for 2 minutes, and a final extension step at 72°C for 5 min. The 293-bp PCR products were electrophoresed on a 1.5% agarose gel at 120 V for 40 minutes.

Following PCR amplification, 2.5 µl of PCR products were digested with 0.5 units of restriction enzyme Ssp1 (New England BioLabs, BioLabs) for 45 min at 37°C. The digested PCR products were analyzed by electrophoresis on a 3% agarose gel. The homozygous wildtype allele (AA) was identified by the presence of 148, 125, and 20 bp, the homozygous variant allele (GG) was confirmed by the presence of fragments of 168- and 125-bp size, whereas the heterozygous variant allele (AG) was identified by the presence of 168-, 148-, 125- and 20-bp fragments (Figure 1b).

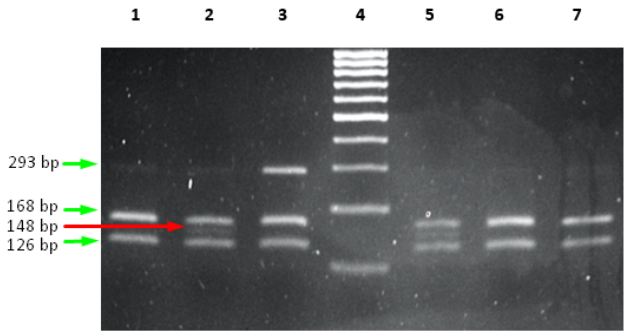


Figure 1(b). Gel electrophoresis for *CYP3A4*18 (digestion enzyme MspI)* and *CYP3A5*3 (digestion enzyme SspI)*. Lane 4 contains a 100-bp ladder. Lanes 2 and 5 indicate a heterozygous individual (*AG*). Lanes 1, 3, 6, 7 show a homozygous mutant individual (*GG*).

## Sequencing

Ten percent of all samples from each different genotype were randomly selected for confirmation via next-generation sequencing. Initially, the PCR products were purified using a QIAGEN QIAquick PCR Purification Kit (QIAGEN, Hilden, Germany) and then dispatched to INTERGEN Laboratory (Ankara, Turkey). In addition, we performed a confirmation sequencing for 10% of all samples related to *CYP3A5*3* allele at Genetic Resources Institute of ANAS via *3130XL* Sanger Sequencing (Applied Biosystems).

## Statistical analysis

The chi-square test ($\chi^2$) was applied to compare the frequencies of polymorphic genotypes and alleles. All the statistical tests were two-sided; the level of significance was taken as $p<0.05$. Statistical analysis was carried out using the SPSS package (ver. 22, SPSS, Chicago, IL).

# RESULTS

One hundred DNA samples from an Azerbaijani population were analyzed, and genotype and allelic frequencies of *CYP3A5*3* and *CYP3A4*18* were determined using the PCR-RFLP method. The frequency of the **3* allele was 0.975 (95 out of 100), with the **1* allele frequency being 0.025 (5 out of 100). The frequency of heterozygote (*CYP3A5*1/*3*) and mutant homozygote (*CYP3A5*3/*3*) genotypes were 0.05 (5/100) and 0.95 (95/100), respectively (Table 1). *CYP3A5*1/*1* was not identified in any of Azerbaijani individuals. According to findings of the given preliminary investigation, 95% of the Azerbaijani population with *CYP3A5*3/*3* may fail to express CYP3A5 protein.

All the volunteers (100/100) were wildtype for the *CYP3A4*18* allele (Table 1).

The given values conformed with the predictions of Hardy-Weinberg equilibrium.

We compared the distribution of allelic and genotype frequencies between the Azerbaijani population in this experiment and other reported ethnic populations (Table 2).

Table 1. Frequencies of CYP3A5 and CYP3A4 variant alleles in the Azerbaijani population.

| Polymorphism | Impact | Allele frequency | | Genotype frequency | | |
|---|---|---|---|---|---|---|
| | | W | M | W/W | W/M | M/M |
| CYP3A5*3 | Splicing effect | 0.025 | 0.975 | 0 (0/100) | 0.05 (5/100) | 0.95 (95/100) |
| CYP3A4*18 | Leu293Pro | 1 | 0 | 1 (100/100) | 0 (0/100) | 0 (0/100) |

Table 2. Chi-square test and P-values of differences in allelic frequencies between Azerbaijani and various ethnic groups.

| Population | Azerbaijani | |
|---|---|---|
| | Chi-square test ($\chi 2$) | P-value |
| African American | 70.736 | <0.01 |
| British | 3.723 | 0.054 |
| Caucasians | 1.196 | 0.274 |
| Chinese | 40.717 | <0.01 |
| Dutch Caucasians | 8.849 | 0.03 |
| Japanese | 42.010 | <0.01 |
| Turkish | 1.347 | 0.246 |

The allelic frequency of *CYP3A5*3* in the Azerbaijani population (97.5%) was significantly higher than Asian populations, including Chinese (77.8%) (Hu et al., 2005) ($\chi^2$=40.717, P<0.01) and Japanese (76.8%) (Fukuen et al., 2002) ($\chi^2$=42.010, P<0.01), Dutch Caucasians (91.7%) (van Schaik et al., 2002) ($\chi^2$=8.849, P=0.03) and African American (47.5%) (Kuehl et al., 2001) ($\chi^2$=70.736, P<0.01), however, relatively similar to British (93.5%) (King et al., 2003) ($\chi^2$=3.723, P=0.054), German and Swiss (95,1%) (Hustert et al., 2001) ($\chi^2$=1.196, P=0.274) and Turkish (96%) (Arıcı and Ozkhan, 2016) ($\chi^2$=1.347, P=0.246). Correspondingly, *CYP3A5*3* heterozygote and mutant homozygote alleles were notably higher than in Chinese ($\chi^2$=28.952, P<0.01), Japanese ($\chi^2$=31.551, P<0.01), and in African American ($\chi^2$=20.188, P<0.01; Table 3).

We performed Sanger sequencing for the complete validation process of the obtained results. Figure 2 illustrates an electropherogram from PCR amplification of the *CYP3A5*3* allele. Each peak represents a single nucleotide in the DNA sequence. As expected, sequencing of the mutant genotype (*CYP3A5*3/*3*) revealed a single base substitution of adenine with a guanine (A>G) in intron 3 (Figure 2(a)), whereas sequencing of the sample with wildtype genotype (*CYP3A5*1/*1*) matched reference sequence (Figure 2(c)) without alterations (Figure 2(b)).

Table 3. Allelic and genotype frequency of CYP3A5 in various populations.

| Ethnicity | n[a] | Allele frequency | | Genotype frequency | | |
|---|---|---|---|---|---|---|
| | | W | M | W/W | W/M | M/M |
| Azerbaijani | 200 | 0.025 | 0.975 | 0 | 5 | 95 |
| British | 200 | 0.065 | 0.935 | 0 | 13 | 87 |
| Turkish | 312 | 0.04 | 0.96 | 0 | 8.97 | 91.03 |
| Caucasians | 366 | 0.049 | 0.951 | n/a | n/a | n/a |
| Chinese | 604 | 0.222 | 0.778 | 7.3 | 29.8 | 62.9 |
| Japanese | 400 | 0.233 | 0.768 | 7 | 32.5 | 60.5 |
| Dutch Caucasians | 1000 | 0.083 | 0.917 | 0.2 | 16.7 | 83.1 |
| African American | 40 | 0.450 | 0.475 | 25 | 25 | 35 |

## DISCUSSION

Being the most abundant isoforms in the liver and intestine, CYP3A4 and CYP3A5 play a crucial role in drug metabolism. Polymorphisms that cause alterations in CYP3A enzyme activity form an interindividual difference in a metabolic profile of a number of drugs that remain constant throughout the lifetime. Homozygosity for the *CYP3A5*3* allele causes almost complete abrogation of *CYP3A5* activity; besides, patients with a *CYP3A5*1* allele have a threefold higher total CYP3A protein. Therefore, CYP3A5 expression may represent about 50% of the total CYP3A hepatic content equal to CYP3A4 activity (Zhou et al., 2017; Saiz-Rodriges et al., 2020). According to the online database of the Human Cytochrome P450 Allele Nomenclature Committee (Sims et al., 2010), more than 70 SNPs of CYP3A4 have been identified.

It is crucial to mention the considerable ethnic variation in the prevalence of CYP3A4 and CYP3A5 variant alleles. *CYP3A4*18* polymorphism was reported in 53% of African Americans and 9% in Caucasians but has not been identified in Azerbaijani and Asian populations (0%) (Hu et al., 2005). Also, we indicated that *CYP3A5*3* allele is abundantly present in the Azerbaijani population with an allele frequency of 0.975. Despite being a small-scale study, our results correspond with previously reported frequencies in Dutch Caucasian, German and Swiss, British, and Turkish populations, demonstrating an allelic frequency of 91 to 96%. For comparison, *CYP3A5*3* allele was less common in Asians and much less frequent in African Americans (Fukuen et al., 2002; van Schaik et al., 2002; Hu et al., 2005, Arıcı and Ozkhan, 2016).

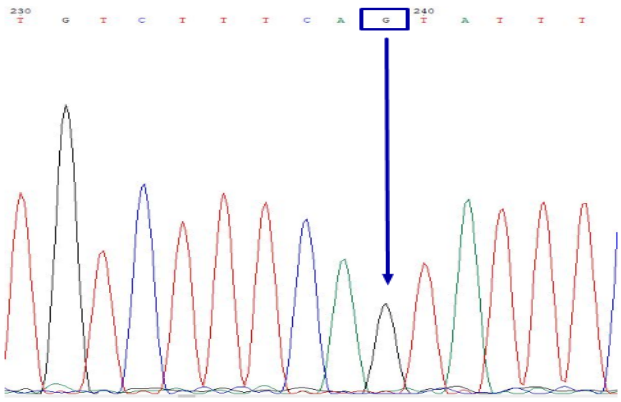

Figure 2(a). Sanger Sequencing results for the CYP3A5 allele. This picture demonstrates a sample with homozygous CYP3A5*3/*3 genotype.

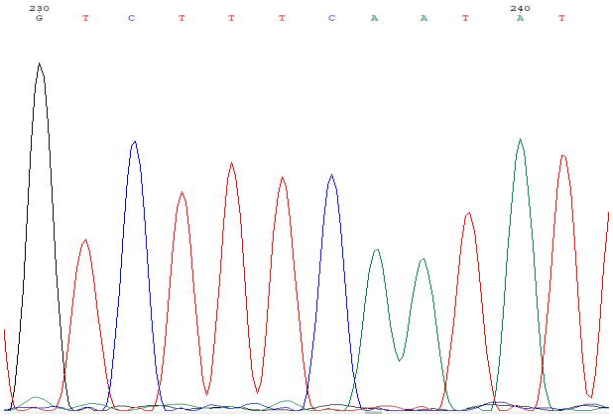


Figure 2(b). Sanger Sequencing results for the CYP3A5 allele. This picture shows a trace for a homozygous wildtype (CYP3A5*1/*1) genotype.

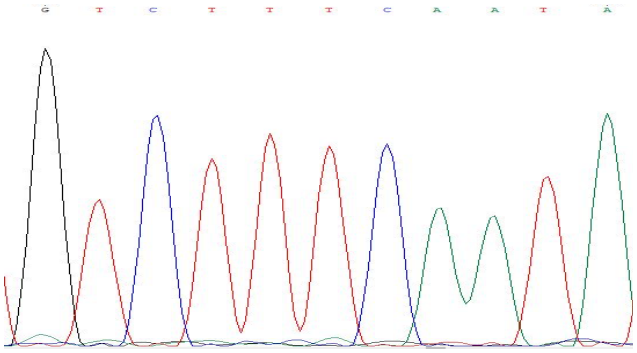

Figure 2(c). Sanger Sequencing results for the CYP3A5 allele. This picture shows a reference sequence.

There are number of recent studies that demonstrates the involvement of *CYP3A5*3* and *CYP3A4*18* polymorphisms in treatment response. Also, the difference in the given SNPs' prevalence may affect drug efficiency and toxicity among various ethnic populations. For instance, *CYP3A4*18* is stated to influence catalytic activities toward various substrates both in vitro and in vivo and play a significant role in the interindividual differences in the pharmacodynamics of therapeutic agents of CYP3A4 substrate in East Asians (Maekawa et al., 2010). As has been reported recently, *CYP3A4*18* is associated with response to Imatinib (IM) therapy in chronic myeloid leukemia (CML) patients in the Azerbaijani population, while CYP3A5*3 has no relationship with the response to IM (Asadov et al., 2019). In contrast with results in the Azerbaijani population, studies in various ethnic populations demonstrated no statistically significant correlation between *CYP3A4*18* and IM response (Gota et al., 2012, Seong et al., 2013, Maddin et al., 2016). However, these results are considered preliminary, and the clinical significance of these SNPs in the Azerbaijani population remains to be further investigated in larger cohorts.

According to the investigation of the correlation between CYP3A5 polymorphism and clopidogrel resistance cases with ischemic heart disease, *CYP3A5*3/*3* carriers had a 2.78 (0.97-7.98; $p<0.05$) fold risk of developing clopidogrel resistance (Priyadharsini et al., 2014). A recent meta-analysis reported that *CYP3A5*3* polymorphism is associated with cyclosporine (CsA) dosage, a calcineurin inhibitor used to prevent allograft rejection in renal transplant recipients, mainly metabolized by CYP3A4 and CYP3A5 isoforms (Zhu et al., 2010). CsA's bioavailability was notably higher in Caucasian American renal transplantation cases than in African American patients, but Caucasian Americans required significantly lower drug dosage compared with African American patients (First et al. 1996). Another relevant study of cyclosporine and tacrolimus in renal transplant subjects in North India (Singh et al., 2009) indicated a significant association between CYP3A5*3 expressers and lower dose-adjusted CsA/Tac concentrations. Namely, the CY3A5 expressers indicated an elevated daily dose requirement at 1 month (7.43±1.58 vs. 7.13±1.56 mg/kg/day, $p=0.131$) and 3 months (4.46±1.26 vs. 4.19±1.22 mg/kg/day, $p=0.003$), compared to the non-expressers. Investigation of the effect of CYP3A5 polymorphism on the metabolic profile of CsA demonstrated that the formation of CsA's primary metabolites AM19 and AM1c9 was lower from incubations with liver and kidney microsomes with *CYP3A5*3/*3* genotype (Dai et al., 2004).

Interestingly, a group of studies evaluating the impact of *CYP3A5*3* polymorphism on the various drugs dosage in the Korean population showed similar results. Namely, Kim et al. investigated an impact of *CYP3A5*3* genotype on a cholesterol-lowering medication, simvastatin. The study reported that after 20mg of the drug, the plasma concentration-time curve (AUC) in the *CYP3A5*3/*3* carriers (16.35 ng*h/mL) was higher than in *CYP3A5*1/*1* carriers (4.94 ng*h/mL). Similarly, with alprazolam, a drug widely used in the treatment of anxiety and panic disorders, which AUC also was found to be significantly greater in patients with *CYP3A5*3/*3* genotype ((830.5 ± 160.4 ng · h/mL [mean± SD]) than in those with *CYP3A5*1/*1* (599.9 ± 141.0 ng · h/mL) (P=.030) (Park et al., 2006). In the case of carbamazepine, a drug to prevent partial seizures, results stated that the oral clearance in CYP3A5 expressers is noteworthy lower than in non-expressers. (Park et al., 2009).

However, despite a number of studies that clearly demonstrate reduced enzyme activity caused by polymorphic *CYP3A5*3*, contradictory findings indicate a lower clearance in normal allele carriers. For instance, the oral clearance of amlodipine, a calcium channel blocker, was higher in the *CYP3A5*3/*3* carriers than in *CYP3A5*1* carriers (P=0.063) (Kim et al., 2006). Another similar study in the Malawian population showed a correlation between *CYP3A5*3* allele and decreased AUC for nevirapine, an antiviral agent (Brown et al., 2012). These findings suggest, despite the clear evidence that *CYP3A5*3* possesses a dysfunctional enzymatic character, *CYP3A5*3* enzyme can still have an elevated activity for some CYP3A substrates. Thus, further population pharmacokinetic research may contribute to mechanism exploration, more accurate dose prediction, and improved therapy.

## Conclusion

In summary, our study describes the *CYP3A4*18* and *CYP3A5*3* genotypes in an Azerbaijani population. This is the first study to investigate polymorphisms of Human Cytochrome P450 families in the Azerbaijani population. We identified *CYP3A4*18* and *CYP3A5*3* alleles and demonstrated that the **3* allele is prevalent in the population while all the study volunteers were revealed to be wildtype for the *18 allele. Thus, the results suggest that 95% of Azerbaijani individuals with *CYP3A5*3/*3* genotype might fail to express CYP3A5 protein. These findings highlight the importance of genotyping of *CYP3A5*3* as it may have crucial clinical implications in therapeutic drug monitoring for individualized therapy. Despite correspondence of our results with similar studies from other populations, this study possesses limitations due to a small number of subjects. Therefore, there is a necessity for future experiments with larger cohorts.

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## Author's contribution

Nigar Karimova and Bayram Bayramov performed laboratory experiments. Aypara Hasanova and Bayram Bayramov played a vital role in data analysis and selection of statistical methodology. Nigar Karimova wrote the manuscript. All authors have read and accepted the final version of the manuscript.

## Conflict of interest

The author has no conflict of interest.

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