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The Frequency of CYP3A5 Expression in a Mexican Population Compared to a Caucasian Population

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JWG, AFH, and RSK designed the study, performed the statistical analysis, and wrote the protocol. Author JWG wrote the first draft of the manuscript. All authors performed the analyses of the study. Authors JWG, AFH, and RSK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the frequencies of the six most common *CYP3A5* alleles and genotypes in a Mexican-American population compared to a non-Hispanic Caucasian population.
Study Design: This cross-sectional study compared the frequency of *CYP3A5* genetic variations in a Mexican-American population compared to a non-Hispanic Caucasian population.
Duration of Study: The study was conducted from September 2014 to April 2015.
Methodology: There were 236 Mexican-American and 237 non-Hispanic Caucasian samples that were analyzed. The two groups of subjects' gDNA were analyzed for *CYP3A5* rs776746 (*3), rs56411402 (*4), rs10264272 (*6), rs41303343 (*7), rs55817950 (*8), and rs28383479 (*9).
Results: There was a significant difference in the *CYP3A5*3* containing diplotypes, but no other diplotypes were significantly different. The frequency of the *CYP3A5*3* allele in the Mexican population was 0.782, which was significantly lower than the frequency of the *CYP3A5*3* allele in the non-Hispanic Caucasian population of 0.932 (P <0.001). The *CYP3A5*7* frequency was very low in the Mexican-American group at 0.85% and was absent in the Caucasian group (P = 0.045).

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Mexican-Americans were three times more likely to be CYP3A5 expressers compared to non-Hispanic Caucasians (P <0.001).
Conclusion: *CYP3A5*3* and *7 allele frequencies vary significantly between Mexicans and non-Hispanic Caucasians, while other allele frequencies for *CYP3A5*4, *6, *8* and **9* do not vary significantly between Mexicans and non-Hispanic Caucasians. Mexican-Americans were shown to have a three-fold higher frequency of CYP3A5 expression compared to non-Hispanic Caucasians.

Keywords: CYP3A5; Mexicans; pharmacokinetics; drug dosing; allele frequency; genotype.

1. INTRODUCTION

The liver is a vital organ in human physiology, and has an important effect on how medications are removed from the body [1]. Many enzymes are synthesized in the liver and metabolize both endogenous and exogenous compounds to help excrete them from the body. Of particular importance in the liver are the cytochrome P450 (CYP450) enzymes which are a superfamily of heme-containing monooxygenases that play an important role in the metabolism of a wide variety of drugs that are used clinically. The CYP450 enzymes are classified into families, subfamilies, and polypeptides. Of particular importance is the CYP3A family of enzymes, because it is the most abundant group of CYP enzymes in the liver and intestines [2]. The CYP3A5 enzyme catalyzes many reactions including the metabolism of certain medications including steroid hormones, maraviroc, tacrolimus, cyclosporine, quetiapine, and vincristine [1-3].

The *CYP3A5* gene is found on chromosome 7q21.12, and a number of different single nucleotide polymorphisms (SNPs) have been identified in *CYP3A5.* Several of these result in the production of splice variants, which cause the protein to become non-functional [3]. Table 1 lists the most common *CYP3A5* variants.

Table 1. *CYP3A5* variant alleles evaluated

Allele	Nucleotide change in gDNA	Effect
*3	6986 A>G	Splicing defect
*4	14665 A>G	Q200R
*6	14690 G>A	Splicing defect
*7	27131_27132insT	346 Frameshift
*8	3699 C>T	R28C
*9	19386 G>A	A337T

The wild-type form of *CYP3A5* is *CYP3A5*1*, which produces functional CYP3A5 enzyme, while *CYP3A5**3, *4, *7, *8, and *9 produce hypofunctional or nonfunctional enzymes. A CYP3A5 expresser is an individual who produces at least some functional CYP3A5 enzyme, as a result of having at least one copy of the *CYP3A5*1* allele [4]. Individuals who possess one (intermediate metabolizer) or two (extensive metabolizer) copies of *CYP3A5*1* will produce a functioning CYP3A5 enzyme. Any individual who does not possess at least one copy of the *CYP3A5*1* allele will not produce properly functioning CYP3A5 enzyme and is known as a non-expresser (poor metabolizer).

The most prevalent allele in the Caucasian population is *CYP3A5*3*, which does not produce functioning CYP3A5 enzyme and as a result only about 10% of Caucasian individuals are CYP3A5 expressers [1]. However, it has been shown that approximately 60% of African-Americans have at least one copy of the *CYP3A5*1* allele and about 45% are homozygous for the *CYP3A5*1* allele [1]. Therefore, African-Americans have a much higher tendency to produce functional CYP3A5 enzyme than Caucasians.

Differing amounts of functional CYP3A5 enzyme affect the rate of drug metabolism and can lead to changes in the concentration of medications in the blood, and therefore a change in efficacy and/or toxicity of the drug. Decreased amounts of functional CYP3A5 enzyme can lead to decreased metabolism of CYP3A5 substrates and elevated drug concentrations in the patient resulting in an increased risk of side effects and toxicity. Higher levels of functional CYP3A5 enzyme can lead to increased metabolism of medications and sub-therapeutic concentrations in the patient [1]. For example, recent evidence suggests that the HIV medication maraviroc, which is metabolized by CYP3A5, may be under dosed in a large portion of the African-American population due to higher frequencies of functional CYP3A5 in African Americans [1]. HIV medications are of significant interest, because of the disease prevalence in minority populations and the fact that some HIV medications (e.g. maraviroc, ritonavir, saquinavir, indinavir) are metabolized by CYP3A5 [1,5-7]. Hispanics make up about 21% of all new HIV diagnoses each

year in the United States and therefore also may require significant dose adjustments [8].

Tacrolimus is an immunosuppressive agent metabolized by CYP3A5 that is used to help patients who are undergoing an organ transplant [9]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has released guidelines to help clinicians with genotype-guided dosing, so that target tacrolimus concentrations can be achieved quicker after transplant [9]. Non-expressers (poor metabolizers) of CYP3A5 are recommended to begin therapy with a "normal" dose of tacrolimus, while known CYP3A5 expressers are recommended to start with an increased dose of tacrolimus to achieve target concentrations quicker [9].

Cyclosporine is another immunosuppressive agent that is metabolized significantly by CYP3A5 [10]. Previous studies have shown that expression of CYP3A5 has been associated with an increased accumulation of the cyclosporine metabolite known as AM19, and this metabolite can lead to nephrotoxic side effects when a large concentration is accumulated [10].

In addition, quetiapine is an antipsychotic medication usually used to treat schizophrenia and manic episodes and has been shown to be influenced by CYP3A5 enzyme expression [11]. A previous study showed that CYP3A5 expression causes pharmacokinetic differences between patients including significantly higher AUC of patients who are non-expressers of CYP3A5 compared to the AUC of patients who express CYP3A5 [11].

Finally, vincristine is metabolized by CYP3A5 and is used to help treat cancer patients, while also demonstrating a potential for significant side effects like neuropathy and neurotoxicity [12]. A previous study has shown a reduced side effect profile when vincristine was given to expressers of CYP3A5 [12]. Interestingly, it has been noted that African-Americans may experience less neurotoxicity than Caucasian patients, which may be due to the increased amount of functional CYP3A5 in African-Americans [12].

Many clinical trials involve a predominantly Caucasian subject population, and evidence from clinical trials is often used to help develop dosing guidelines for many medications [13-18]. Therefore, many current medication dosing guidelines for CYP3A5 substrates may be established from primarily Caucasian allele frequencies and genotypes of *CYP3A5*. The Caucasian population has a substantial difference in the frequency of *CYP3A5* alleles and genotypes when compared to many other ethnicities [19-21]. Thus, some medications will likely need to be dose adjusted for patients of other ethnic groups based on an individual patient's *CYP3A5* genotype [9].

Currently, Hispanics are the largest minority in the United States, and there is little information about the frequencies of alleles and genotypes of *CYP3A5* in the Mexican-American population [8]. Marsh, et al. [22] evaluated allele frequencies between Mexican and Peruvian populations and found a 5% difference in one mutation (*3C, rs776746) for *CYP3A5*. In addition, Claudio-Campos, et al. determined that the most common variant allele in the Hispanic population is the *CYP3A5*3* allele [23]. This study aims to determine the frequencies of the six most common *CYP3A5* alleles and genotypes in a Mexican-American population compared to a non-Hispanic Caucasian population.

2. METHODOLOGY

This cross-sectional study compared the frequency of *CYP3A5* genetic variations in a Mexican-American population compared to a non-Hispanic Caucasian population. The study was conducted from September 2014 to April 2015. A total of 473 subjects' DNA were analyzed for different SNPs. Previously recruited samples of Mexican and non-Hispanic Caucasian DNA were analyzed in the study. The Mexican subjects were recruited from two separate Mexican Consulate health fair events held at Shenandoah University. Recruitment included an informed consent in Spanish as well as a brief questionnaire to confirm Mexican ancestry for at least the last two generations. The control subjects were recruited from a local primary care clinic and all were self-reported as Caucasian. Genomic DNA (gDNA) was isolated from buccal swabs using a DNA Blood Minikit on a Qiacube workstation (Qiagen; Valencia, CA, USA). The authors analyzed 236 Mexican and 237 non-Hispanic Caucasian samples. The two groups of subjects' gDNA were analyzed for *CYP3A5* rs776746 (*3), rs56411402 (*4), rs10264272 (*6), rs41303343 (*7), rs55817950 (*8), and rs28383479 (*9). The assay mix included non-labeled primers and proprietary fluorescent TaqMan MGB VIC and FAM labeled oligonucleotide probes, one for the wild-type

allele and one for the specific variant allele (ThermoFisher Applied Biosystems; Foster City, CA, USA). Genotyping of samples was performed on an Applied Biosystems 7300 real-time PCR under conditions specified by the manufacturer.

CYP3A5 expressers were defined as having at least one copy of the *CYP3A5*1* allele, and non-expressers were defined as the absence of a *CYP3A5*1* allele. Allele counting and Chi-square analysis were used to test Hardy-Weinberg equilibrium. Genotype comparisons were done using a Chi-square test and when applicable a Fischer's Exact test using SPSS v21 (IBM analytics, Armonk, New York). A *P* value of less than 0.05 was deemed to be statistically significant. This study was approved by the Shenandoah University IRB prior to its commencement in September 2014.

3. RESULTS

A total of 236 Mexicans and 237 Caucasian samples were genotyped. All alleles and genotypes were determined to be in Hardy-Weinberg equilibrium with a *P* value greater than 0.05. Table 2 presents the *CYP3A5* diplotypes of the Mexican-American and the non-Hispanic Caucasian subjects. There was a significant difference in the *CYP3A5*3* containing diplotypes, but no other diplotypes were significantly different. The frequency of the *CYP3A5*3* allele in the Mexican population was 0.782, which was significantly lower than the frequency of the *CYP3A5*3* allele in the Caucasian population of 0.932 (*P* <0.001) as shown in Table 3. The *CYP3A5*7* frequency was very low in the Mexican-American group at 0.85% and was absent in the Caucasian group (*P* = 0.045). Finally, the CYP3A5 expresser statuses of the two groups are presented in Table 4. The Mexican-Americans were three times more likely to be CYP3A5 expressers with 36% of Mexicans being expressers whereas only 12% of Caucasians were CYP3A5 expressers (*P* <0.001).

4. DISCUSSION

The results of this study show that the frequency of the *CYP3A5*3* allele varies significantly between these Mexican and non-Hispanic Caucasian groups. The much higher frequency of the *CYP3A5*3* allele in the Caucasian population resulted in a large portion of the group being non-expressers of the CYP3A5 enzyme. The frequency of the *CYP3A5*7* allele also varied significantly between the two groups. However, the frequencies of *CYP3A5*4, *6, *8,* and **9* were not significantly different between the two groups. The low incidence of the *CYP3A5*4, *6, *7, *8,* and **9* alleles is similar to previous studies of the non-Hispanic Caucasian population [3,24]. Therefore, the *CYP3A5*3* allele is an important variant allele for determination of CYP3A5 expresser status in the Mexican population just as it is in the Caucasian

Table 2. Comparison of the *CYP3A5* diplotypes

***CYP3A5* diplotypes**	**Mexican group total N = 236**	**Caucasian group total N = 237**	***P* value**
*1/*1	11	2	<0.001
*1/*3	80	28	
*3/*3	145	207	
*1/*1	236	237	N/A
*1/*4	0	0	
*4/*4	0	0	
*1/*1	233	235	0.69
*1/*6	3	2	
*6/*6	0	0	
*1/*1	232	237	0.06
*1/*7	4	0	
*7/*7	0	0	
*1/*1	236	237	N/A
*1/*8	0	0	
*8/*8	0	0	
*1/*1	236	237	N/A
*1/*9	0	0	
*9/*9	0	0	

Table 3. Comparison of the *CYP3A5* Variant Allele Frequencies

CYP3A5 variant allele	Mexican group N = 472 N (%)	Caucasian group N = 474 N (%)	*P* value
*3	369 (78.2%)	442 (93.2%)	<0.001
*4	0	0	N/A
*6	3 (0.64%)	2 (0.42%)	0.65
*7	4 (0.85%)	0	0.045
*8	0	0	NA
*9	0	0	NA

Table 4. Comparison of the CYP3A5 expresser frequencies

CYP3A5 enzyme expression*	Mexican group N = 236 N (%)	Caucasian group N = 237 N(%)
expresser	85 (36.0%)	28 (11.8%)
non-expressers	151 (64.0%)	209 (88.2%)

p-value = < 0.001

** expresser = At least one copy of *1 allele, non-expresser = no *1 allele*

population. Genomic testing would not be a cost-effective strategy for the *CYP3A5*4, *6, *8,* and **9* variants due to their extremely low incidence [25]. The *CYP3A5*7* allele has very low frequency but does exist in the Mexican population.

There is both a statistical and clinically significant difference between the frequency of CYP3A5 expression in the Caucasian and Mexican-American populations, which has implications for dosing of CYP3A5 substrates. Mexican-Americans have a three-fold higher frequency of expression of the CYP3A5 enzyme compared to Caucasians. The higher frequency of CYP3A5 expression in the Mexican-American population could result in an increased probability of lower concentrations of medications primarily metabolized by CYP3A5.

Dose finding studies are often conducted in a Caucasian subject population. For example, the MOTIVATE trial for maraviroc was comprised of approximately 80% Caucasians [1]. As a result patients who express more functional CYP3A5 could have a decreased efficacy of maraviroc, and these patients could receive suboptimal therapy. It has been shown that the AUC of maraviroc is significantly affected based on expression or lack of expression of CYP3A5 in African-American subjects [1]. CYP3A5 expressers have been shown to have an approximate 50% reduction in maraviroc AUC compared to non-expressers. The lower AUC of maraviroc would not allow for effective drug concentrations to be reached and as a result the patient could be receiving suboptimal care. Resistance can also develop to HIV medications when the proper therapeutic drug concentrations are not reached [26,27]. In this study, the higher tendency to express CYP3A5 in Mexican-Americans is consistent with findings in an African-American population, which could result in sub-therapeutic concentrations of medications highly dependent on CYP3A5 metabolism such as maraviroc which is especially important for the Mexican-American population due to a higher HIV frequency [8].

Additionally, the expression of CYP3A5 is important when trying to achieve tacrolimus drug concentrations quickly. Since, Mexican-Americans have a higher tendency to express functioning CYP3A5 than non-Hispanic Caucasians it may be beneficial to use genotype guided initial dosing for these individuals, since they may require an increased initial dose of tacrolimus. Faster achievement of target concentrations may help to reduce complications of organ transplant rejection [9]. However, further studies are needed to assess the clinical outcomes from faster achievement of target concentrations.

CYP3A5 expression is also important for cyclosporine. A higher frequency of functional CYP3A5 in the Mexican population could be relevant for potential side effects with cyclosporine [10]. Mexican-Americans could have a greater tendency to create the nephrotoxic metabolite AM19 compared to non-Hispanic Caucasians due to the higher tendency to produce functional CYP3A5 [10]. Thus, Mexican patients may need to be genotyped prior to the addition of cyclosporine to their medication regimen or they may need extra monitoring to ensure that they do not overproduce the nephrotoxic metabolite.

Table 5. Summary of medications influenced by CYP3A5 enzyme expression

Medication	Effect of increased CYP3A5 enzyme expression
Maraviroc	Reduced AUC and potential for drug resistance and reduced efficacy
Cyclosporine	Potential for increased formation of nephrotoxic AM19 metabolite
Quetiapine	Reduced AUC and potential for subtherapeutic concentrations and reduced efficacy
Vincristine	Potential reduction in nuerotoxicity

Another example of a medication that could be inappropriately dosed is quetiapine, because expressers have been shown to have a decreased quetiapine AUC compared to non-expressers [11]. Therefore, expressers of CYP3A5 could be receiving sub-therapeutic doses of quetiapine and not experiencing the full benefit of the medication. Mexican-Americans who are being treated with quetiapine would be less likely to experience the full benefit of the medication compared to non-Hispanic Caucasians, and thus it may be necessary to increase the dose for Mexicans who are expressers of CYP3A5. If Mexican patients receive sub-therapeutic concentrations of quetiapine it is possible that their schizophrenia or manic episodes may not respond appropriately leading to worse outcomes.

Neurotoxicity is often associated with vincristine, and is especially common with patients who are non-expressers of the CYP3A5 enzyme. In a previous study, African-Americans had an 11% lower incidence of neurotoxicity compared to Caucasians [12]. The increased tendency to express CYP3A5 may be contributing to this decreased amount of neurotoxicity seen in patients using vincristine [12]. A similar result may be expected for Mexican patients due to their increased frequency of CYP3A5 expression. Thus, Mexican-American patients may experience less neurotoxicity when given vincristine than non-Hispanic Caucasians [12,28]. Mexican patients may be able to better handle increased doses of vincristine leading to better outcomes, because the dose does not have to be stopped due to neurotoxicity [12]. A previous study also found that African-Americans had fewer missed vincristine doses and fewer vincristine doses reduced than Caucasians [12]. Therefore, vincristine may be a safer option in the Mexican population than in the non-Hispanic Caucasian population due to the reduced potential for neurotoxicity [28]. Table 5 summarizes these potential medication effects.

5. CONCLUSION

*CYP3A5*3* and *7 allele frequencies vary significantly between Mexicans and non-Hispanic Caucasians, while other allele frequencies for *CYP3A5*4, *6, *8* and **9* do not vary significantly between Mexicans and non-Hispanic Caucasians. Mexican-Americans were shown to have a three-fold higher frequency of CYP3A5 expression compared to non-Hispanic Caucasians. The increased expression of functional CYP3A5 enzyme in the Mexican population may warrant dosage adjustments to achieve therapeutic concentrations of medications metabolized primarily through CYP3A5, thus preventing side effects and maintaining efficacy. In the future, CYP3A5 genotyping all patients may be beneficial to determine the proper initial dose of medications metabolized by CYP3A5.

CONSENT

All authors have declared that written informed consent was obtained from all the participants.

ETHICAL APPROVAL

This study was approved by the Shenandoah University IRB prior to its commencement in September 2014.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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