

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

## 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), 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 ( $P = 0.045$ ). 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 an important organ in the body, 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 maraviroc, tacrolimus, cyclosporine, quetiapine, and vincristine [1,2].

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.

29 **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           |

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

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

43 Differing amounts of functional *CYP3A5* enzyme affect the rate of drug metabolism and can lead to  
 44 changes in the concentration of medications in the blood, and therefore a change in efficacy and/or  
 45 toxicity of the drug. Decreased amounts of functional *CYP3A5* enzyme can lead to decreased metabolism  
 46 of *CYP3A5* substrates and elevated drug concentrations in the patient resulting in an increased risk of  
 47 side effects and toxicity. Higher levels of functional *CYP3A5* enzyme can lead to increased metabolism  
 48 of medications and sub-therapeutic concentrations in the patient [1]. For example, recent evidence  
 49 suggests that the HIV medication maraviroc, which is metabolized by *CYP3A5*, may be under dosed in a  
 50 large portion of the African-American population due to higher frequencies of functional *CYP3A5* in  
 51 African Americans [1]. HIV medications are of significant interest, because of the disease prevalence in  
 52 minority populations and the fact that some HIV medications (e.g. maraviroc, ritonavir, saquinavir,  
 53 indinavir) are metabolized by *CYP3A5* [1,5-7]. Hispanics make up about 21% of all new HIV diagnoses  
 54 each year in the United States and therefore also may require significant dose adjustments [8].

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

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

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

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

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

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

92  
93 This cross-sectional study compared the frequency of CYP3A5 genetic variations in a Mexican-American  
94 population compared to a non-Hispanic Caucasian population. The study was conducted from  
95 September 2014 to April 2015. A total of 473 subjects' DNA were analyzed for different SNPs. Previously  
96 recruited samples of Mexican and non-Hispanic Caucasian DNA were analyzed in the study. Genomic  
97 DNA (gDNA) was isolated from buccal swabs using a DNA Blood Minikit on a Qiacube workstation  
98 (Qiagen; Valencia, CA, USA). There were 236 Mexican and 237 non-Hispanic Caucasian samples that  
99 were analyzed. The two groups of subjects' gDNA were analyzed for CYP3A5 rs776746 (\*3),  
00 rs56411402 (\*4), rs10264272 (\*6), rs41303343 (\*7), rs55817950 (\*8), rs28383479 (\*9). The assay mix  
01 included non-labeled primers and proprietary fluorescent TaqMan MGB VIC and FAM labeled  
02 oligonucleotide probes, one for the wild-type allele and one for the specific variant allele (ThermoFisher  
03 Applied Biosystems; Foster City, CA, USA). Genotyping of samples was performed on an Applied  
04 Biosystems 7300 real-time PCR under conditions specified by the manufacturer.

05 CYP3A5 expressers were defined as having at least one copy of the CYP3A5\*1 allele, and non-  
06 expressers were defined as the absence of a CYP3A5\*1 allele. Allele counting and Chi-square analysis  
07 were used to test Hardy-Weinberg equilibrium. Genotype comparisons were done using a Chi-square test  
08 and when applicable a Fischer's Exact test using SPSS v21 (IBM analytics, Armonk, New York). A P  
09 value of less than 0.05 was deemed to be statistically significant. This study was approved by the  
0 Shenandoah University IRB prior to its commencement in September 2014.  
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we analyzed 236 ...

### 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 ( $P < 0.001$ ).

**Table 2.** Comparison of the CYP3A5 diplotypes.

| CYP3A5<br>diplotypes | Mexican Group<br>Total N = 236<br>N | Caucasian Group<br>Total N = 237<br>N | 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   |     |

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

| <i>CYP3A5</i><br>Variant Allele | Mexican Group<br>N = 472<br>N (%) | Caucasian Group<br>N = 474<br>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      |

128

129 **Table 4.** Comparison of the *CYP3A5* Expresser Frequencies

| <i>CYP3A5</i><br>enzyme expression* | Mexican Group<br>N = 237<br>N (%) | Caucasian Group<br>N = 236<br>N (%) |
|-------------------------------------|-----------------------------------|-------------------------------------|
| expresser                           | 85 (36.0%)                        | 28 (11.8%)                          |
| non-expressers                      | 151 (64.0%)                       | 209 (88.2%)                         |

130

p-value = < 0.001

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

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#### 4. DISCUSSION

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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

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138 groups. The low incidence of the CYP3A5\*4, \*6, \*7, \*8, and \*9 alleles is similar to previous studies of the  
139 non-Hispanic Caucasian population [3,24]. Therefore, the CYP3A5\*3 allele is an important variant allele  
140 for determination of CYP3A5 expresser status in the Mexican population just as it is in the Caucasian  
141 population. Genomic testing would not be a cost-effective strategy for the CYP3A5\*4, \*6, \*8, and \*9  
142 variants due to their extremely low incidence [25]. The CYP3A5\*7 allele has very low frequency but does  
143 exist in the Mexican population.

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

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

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

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

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

183 Neurotoxicity is often associated with vincristine, and is especially common with patients who are non-  
184 expressers of the CYP3A5 enzyme. In a previous study, African-Americans had an 11% lower incidence  
185 of neurotoxicity compared to Caucasians [12]. The increased tendency to express CYP3A5 may be  
186 contributing to this decreased amount of neurotoxicity seen in patients using vincristine [12]. A similar  
187 result may be expected for Mexican patients due to their increased frequency of CYP3A5 expression.

188 Thus, Mexican-American patients may experience less neurotoxicity when given vincristine than non-  
 189 Hispanic Caucasians [12,28]. Mexican patients may be able to better handle increased doses of  
 190 vincristine leading to better outcomes, because the dose does not have to be stopped due to  
 191 neurotoxicity [12]. A previous study also found that African-Americans had fewer missed vincristine doses  
 192 and fewer vincristine doses reduced than Caucasians [12]. Therefore, vincristine may be a safer option in  
 193 the Mexican population than in the non-Hispanic Caucasian population due to the reduced potential for  
 194 neurotoxicity [28].

## 195 5. CONCLUSION

196  
 197 CYP3A5\*3 and \*7 allele frequencies vary significantly between Mexicans and non-Hispanic Caucasians,  
 198 while other allele frequencies for CYP3A5\*4, \*6, \*8 and \*9 do not vary significantly between Mexicans and  
 199 non-Hispanic Caucasians. Mexican-Americans were shown to have a three-fold higher frequency of  
 200 CYP3A5 expression compared to non-Hispanic Caucasians. The increased expression of functional  
 201 CYP3A5 enzyme in the Mexican population may warrant dosage adjustments to achieve therapeutic  
 202 concentrations of medications metabolized primarily through CYP3A5, thus preventing side effects and  
 203 maintaining efficacy. In the future, CYP3A5 genotyping all patients may be beneficial to determine the  
 204 proper initial dose of medications metabolized by CYP3A5.

## 205 CONSENT

206  
 207 All authors have declared that written informed consent was obtained from all the participants.

## 208 ETHICAL APPROVAL

209  
 210 This study was approved by the Shenandoah University IRB prior to its commencement in September  
 211 2014.

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