ORIGINAL ARTICLE

Frequency of *CYP3A5* alleles in pediatric patients with advanced chronic kidney disease and kidney transplant recipients at a national referral center in Lima, Peru

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ABSTRACT

Objective: To determine the frequency of the *CYP3A5**1 and *CYP3A5**3 alleles in pediatric patients with advanced chronic kidney disease and kidney transplant recipients treated at a national referral center in Lima, Peru.
Methods: This was a descriptive, observational study. Patients with advanced chronic kidney disease (stages 3a, 3b, and 5) and kidney transplant recipients treated at the Instituto Nacional de Salud del Niño San Borja between February 2019 and January 2020 were included. *CYP3A5**3 polymorphism genotyping was performed using PCR-RFLP. Data were analyzed using Stata version 15.
Results: A total of 50 patients were included. Twenty-seven patients (54.0%) were male, and the median age was 13.1 years (IQR: 8.6–14.9). The frequency of the *CYP3A5**1 allele was 86.0%, whereas that of the *CYP3A5**3 allele was 14.0%. Overall, 72.0% of the population (n = 36) had the *CYP3A5**1/*1 genotype, whereas 28.0% (n = 14) had the *CYP3A5**1/*3 genotype. The *CYP3A5**3/*3 genotype was not observed.
Conclusions: The *CYP3A5**1 allele was the most frequent in the analyzed population. The *CYP3A5**3/*3 genotype, associated with the CYP3A5 non-expressor phenotype, was not observed. These results should be confirmed in future studies with larger sample sizes and complementary molecular techniques to strengthen the reliability of the findings.

Keywords: Renal Insufficiency, Chronic; Kidney Transplantation; Tacrolimus; Cytochrome P-450 CYP3A; Polymorphism, Genetic; Child (Source: MeSH)

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Frecuencia de los alelos *CYP3A5* en pacientes pediátricos con enfermedad renal crónica avanzada y receptores de trasplante renal en un centro de referencia nacional en Lima, Perú

RESUMEN

Objetivo: Determinar la frecuencia de los alelos *CYP3A5**1 y *CYP3A5**3 en pacientes pediátricos con enfermedad renal crónica avanzada y trasplante renal atendidos en un centro de referencia nacional en Lima, Perú.
Métodos: Estudio observacional descriptivo. Se incluyeron pacientes con enfermedad renal crónica avanzada (estadios 3a, 3b y 5) y pacientes que recibieron un trasplante renal, atendidos en el Instituto Nacional de Salud del Niño San Borja entre febrero de 2019 y enero de 2020. La genotipificación del polimorfismo *CYP3A5**3 se realizó mediante PCR-RFLP. El análisis de los datos se realizó con Stata versión 15.
Resultados: Se incluyeron 50 pacientes. Veintisiete pacientes (54,0 %) fueron de sexo masculino y la mediana de edad fue de 13,1 años (RIC: 8,6–14,9). La frecuencia del alelo *CYP3A5**1 fue del 86,0 %, mientras que la del alelo *CYP3A5**3 fue del 14,0 %. El 72,0 % de la población (n = 36) presentó el genotipo *CYP3A5**1/*1, mientras que el 28,0 % (n = 14) presentó el genotipo *CYP3A5**1/*3. No se observó el genotipo *CYP3A5**3/*3.

Conclusiones: El alelo *CYP3A5**1 fue el más frecuente en la población analizada. No se observó el genotipo *CYP3A5**3/*3, asociado al fenotipo no expresor de la enzima CYP3A5. Estos resultados deben ser corroborados en estudios futuros con un mayor tamaño muestral y mediante técnicas moleculares complementarias que permitan fortalecer la confiabilidad de los hallazgos.

Palabras clave: Insuficiencia Renal Crónica; Trasplante de Riñón; Tacrolimus; Citocromo P-450 CYP3A; Polimorfismo Genético; Niño (Fuente: DeCS)

INTRODUCTION

Kidney transplantation represents the best therapeutic alternative for patients with advanced chronic kidney disease, as it increases survival and quality of life compared with dialysis therapy (1). In this context, tacrolimus is one of the most widely used immunosuppressants for preventing acute graft rejection; however, it has a narrow therapeutic range and high interindividual pharmacokinetic variability, which increases the risk of subtherapeutic or supratherapeutic concentrations (2,3).

Tacrolimus concentration variability is influenced by multiple factors, including age, clinical status, and genetic variability in metabolizing enzymes of the cytochrome P450 system, particularly those belonging to the CYP3A subfamily (CYP3A4 and CYP3A5) (3,4). Among these, CYP3A5 plays a key role in tacrolimus metabolism.

The *CYP3A5**3 polymorphism (g.6986A>G, rs776746) produces a nonfunctional enzyme due to a defect in messenger RNA processing, thereby determining differences in metabolic capacity among individuals. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (5), individuals carrying at least one functional *CYP3A5**1 allele require higher initial tacrolimus doses than non-expressors (*CYP3A5**3/*3), highlighting the clinical importance of this polymorphism in treatment individualization.

In adults, a high frequency of the *CYP3A5**3 allele has been reported, along with substantial variability in its distribution across different ethnic groups. For example, the frequency of this allele has been described as ranging from approximately 14.0% in African populations to more than 90% in European populations, showing a marked gradient according to genetic ancestry (6).

However, most of the available evidence comes from studies in adults. In contrast, information remains limited in pediatric patients with advanced chronic kidney disease or those undergoing kidney transplantation, despite evidence that the *CYP3A5* genotype significantly influences tacrolimus pharmacokinetics in children (3,7,8). In this context, this study aimed to determine the frequency of the *CYP3A5**1 and *CYP3A5**3 alleles in pediatric patients with advanced chronic kidney disease and kidney transplant recipients treated at a national referral center in Lima, Peru.

METHODS

Study design and population

An observational, descriptive, cross-sectional study was conducted, including patients younger than 18 years with a diagnosis of advanced chronic kidney disease, as well as patients who had received a kidney transplant, treated at the Instituto Nacional de Salud del Niño San Borja between February 2019 and January 2020.

The sample consisted of all eligible patients during the 2019–2020 period.

Blood sample collection and DNA isolation

Peripheral blood samples were collected in 3-mL EDTA tubes during scheduled sample collection in the outpatient area of the Pediatric Nephrology Department. DNA was isolated using the commercial NucleoSpin® Blood kit (Macherey-Nagel, Düren, Germany), according to the manufacturer's instructions. DNA concentration (in ng/µL) was determined by fluorometry using the commercial DeNovix dsDNA Broad Range Assays kit (DeNovix, Wilmington, DE, USA). Once isolated, DNA was stored at −20 °C until analysis.

Polymorphism analysis by PCR-RFLP

Detection of the *CYP3A5**3 polymorphism was performed using polymerase chain reaction coupled with restriction fragment length polymorphism analysis (PCR-RFLP). The amplification reaction was carried out in a final volume of 25 µL using a Veriti™ 96-Well Thermal Cycler (Applied Biosystems, Foster City, CA, USA).

Two PCR-RFLP assays were performed for each sample, using different restriction enzymes. The amplification conditions were as follows: initial denaturation at 95 °C for 4 minutes, followed by 37 cycles of denaturation at 95 °C for 30 seconds, annealing at 56 °C for 30 seconds, and extension at 72 °C for 30 seconds, with a final extension at 72 °C for 5 minutes.

In the first assay, a 197-base-pair (bp) fragment of intron 3 of the *CYP3A5* gene was amplified following the method described by Lee et al. (9). The CYP3A5F (5'-CTTTAAAGAGCTCTTTTGTCTCTCA-3') and CYP3A5R1 (5'-GAAGCCAGACTTTGATCATTATGTTATG-3') primers were used. The amplified product was digested with the BseMII restriction enzyme (New England Biolabs, Ipswich, MA, USA), according to the manufacturer's instructions.

In the second assay, a 200-bp fragment of the same intron was amplified according to the method described by Lee et al. (9). The same forward primer and the reverse primer CYP3A5R2 (5'-CCAGGAAGCCAGACTTTGAT-3') were used. The amplified product was digested with the DdeI restriction enzyme (New England Biolabs, Ipswich, MA, USA), according to the manufacturer's instructions.

The digestion products were analyzed by electrophoresis on a 2% agarose gel. A total of 12 µL of the PCR product and 2 µL of intercalating agent (SYBR Green) were used. Electrophoresis was performed for 30 minutes at 90 V. DNA bands were visualized under ultraviolet light using a transilluminator.

Genotypes were assigned according to the fragment patterns obtained after enzymatic digestion, based on the schemes previously described by Lee et al. and Fukuen et al. (10,11) (Supplementary Table 1).

Operational definitions and statistical analysis

Chronic kidney disease was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (12). For clinical characterization of the population, the following variables were considered: age, sex, clinical diagnosis, stage of advanced chronic kidney disease, dialysis modality in patients with stage 5 advanced chronic kidney disease, history of kidney transplantation, transplant origin, donor type, and dialysis modality before transplantation.

Statistical analysis was performed using Stata version 15 (StataCorp LLC, College Station, TX, USA).

To describe the study population, absolute and relative frequencies were calculated for categorical variables, whereas age was summarized using the median and interquartile range (IQR).

Based on the PCR-RFLP analysis results, the frequencies of the *CYP3A5**1 and *CYP3A5**3 alleles, as well as of the *CYP3A5**1/*1, *CYP3A5**1/*3, and *CYP3A5**3/*3 genotypes, were calculated.

Genotype distribution was assessed using the Hardy-Weinberg equilibrium with the chi-square (χ^2) goodness-of-fit test. A p-value < 0.05 was considered statistically significant.

Ethical considerations

Each patient was identified using a numerical code to ensure anonymity. Data confidentiality was protected by restricting database access exclusively to the research team.

The study was approved by the Research Ethics Committee of the Instituto Nacional de Salud del Niño San Borja (code: PI-211-2018). Patient participation was authorized through written informed consent signed by parents or legal guardians and, when appropriate, through assent from minors.

RESULTS

The characteristics of the 50 patients included in the study are summarized in Table 1. The median age was 13.1 years (IQR: 8.6–14.9). Twenty-seven patients (54.0%) were male. According to clinical diagnosis, 5 patients (10.0%) had stage 3a advanced chronic kidney disease, 4 (8.0%) had stage 3b, 9 (18.0%) had stage 5, and 32 (64.0%) had received a kidney transplant. Among patients with stage 5 advanced chronic kidney disease, 4 were receiving peritoneal dialysis, and 5 were receiving hemodialysis. In the group of patients who had received a kidney transplant, most procedures were performed within the institution; among these, transplantation from deceased donors predominated.

The results of PCR-RFLP analysis are summarized in Table 2 and Supplementary Table 2. The observed genotype distribution did not deviate from the Hardy-Weinberg equilibrium (p > 0.05).

Table 1. Sociodemographic and clinical characteristics of the patients included in the study (n = 50)

Characteristic	n (%)
Age, median (IQR), years	13.1 (8.6–14.9)
Sex (male to female)	27:23
Clinical diagnosis	
Advanced chronic kidney disease stage 3a	5 (10.0)
Advanced chronic kidney disease stage 3b	4 (8.0)
Advanced chronic kidney disease stage 5	9 (18.0)
Dialysis modality	
Peritoneal dialysis	4 (44.4)
Hemodialysis	5 (55.6)
Kidney transplantation	32 (64.0)
Transplant origin	
External	2 (6.3)
Internal	30 (93.8)
Donor type	
Living donor	8 (26.7)
Deceased donor	22 (73.3)
Dialysis modality before transplantation	
Peritoneal dialysis	14 (46.7)
Hemodialysis	16 (53.3)

IQR: interquartile range. Percentages for the main clinical diagnoses were calculated based on the total sample (n = 50). Percentages for subcategories were calculated based on the corresponding total of the immediate main category.

Table 2. Frequency of alleles and genotypes in the patients included in the study

Characteristic	n (%)
Allele (2n = 100)	
*CYP3A5**1	86 (86.0)
*CYP3A5**3	14 (14.0)
Genotype (n = 50)	
*CYP3A5**1/*1	36 (72.0)
*CYP3A5**1/*3	14 (28.0)
*CYP3A5**3/*3	0 (0.0)

*CYP3A5**1/*1 and *CYP3A5**1/*3 correspond to expressor phenotypes; *CYP3A5**3/*3 corresponds to the non-expressor phenotype.

All patients carried at least one functional *CYP3A5**1 allele. The allelic frequency of *CYP3A5**1 was 86.0%, whereas the allelic frequency of *CYP3A5**3 was 14.0%. Regarding genotype distribution, 72.0% of the population (n = 36) had the *CYP3A5**1/*1 genotype, whereas 28.0% (n = 14) had the *CYP3A5**1/*3 genotype. The *CYP3A5**3/*3 genotype was not observed.

DISCUSSION

This study provides an initial description of the *CYP3A5**1 and *CYP3A5**3 allelic frequencies in a Peruvian pediatric population with advanced chronic kidney disease and kidney transplantation, in which the functional *CYP3A5**1 allele predominated and the *CYP3A5**3/*3 genotype was absent.

Tacrolimus exposure in pediatric patients who have received a kidney transplant is influenced by multiple clinical factors, including age and concomitant use of other medications, as well as by genetic factors (13–15). CYP3A5 expression has been reported to account for approximately 16.3% of the variability in tacrolimus concentrations, and when considered together with clinical factors, such as erythrocyte count and albumin, the explained proportion reaches 43.3% (16).

From a pharmacogenetic perspective, CYP3A5 expressors require higher doses of tacrolimus to maintain therapeutic concentrations compared with non-expressors (17). In pediatric patients, a meta-analysis in kidney transplant recipients showed significant differences in dose-adjusted trough concentration and daily tacrolimus requirements between patients with the *CYP3A5**3/*3 genotype and those carrying at least one *CYP3A5**1 allele (3).

Consistent with this evidence, the CPIC guidelines recommend adjusting the initial dose of tacrolimus according to *CYP3A5* genotype, considering that patients carrying at least one functional allele (*CYP3A5**1) require higher initial doses. In contrast, individuals with the *CYP3A5**3/*3 genotype do not require the initial dose increase recommended for expressors. This aspect supports the relevance of genotyping in patients who are candidates for kidney transplantation or kidney transplant recipients. In this context, determining the frequency of the *CYP3A5**3 allele in this patient population in Peru and contrasting these findings with those reported in other populations worldwide is relevant for contextualizing the distribution of metabolic phenotypes associated with tacrolimus.

Studies on *CYP3A5* allele frequencies in pediatric populations are limited and include kidney transplant patients from cohorts in Chile, Guatemala, Europe, and the United States (7,8,18,19). The findings of this study differ considerably from those reports, in which a predominance of the *CYP3A5**3 allele has been described, with frequencies ranging from 44% to 80%, compared with the functional *CYP3A5**1 allele, whose frequencies range from 20% to 56%, regardless of the origin of the analyzed population. Consistently, these studies have reported a higher frequency of the *CYP3A5**3/*3 genotype, followed by *CYP3A5**1/*3 and *CYP3A5**1/*1, in that order, with frequencies for the *CYP3A5**3/*3 genotype ranging from 62.5% to 75.7%. In contrast, no individuals with the *CYP3A5**3/*3 genotype were identified in the study population.

In adults, the distribution of allelic and genotypic frequencies is similar to that observed in pediatric populations, although with marked differences according to the origin of the study population (20–31). In this age group, the frequency of the *CYP3A5**3 allele ranges from 63.4% to 85.5%, whereas that of the functional *CYP3A5**1 allele ranges from 14.5% to 36.6%. Likewise, the frequencies of the *CYP3A5**1/*1, *CYP3A5**1/*3, and *CYP3A5**3/*3 genotypes range from 1.3% to 41%, 22% to 41.6%, and 9% to 72.4%, respectively, values that also differ from those observed in the population of the present study.

Globally, the *CYP3A5**3/*3 genotype has been reported to be more frequent in populations of European and Asian origin, whereas the *CYP3A5**1/*1 genotype is observed more frequently in populations of African origin (32). In studies conducted in pediatric and adult patients with kidney transplantation or chronic kidney disease, the *CYP3A5**3/*3 genotype is observed more frequently in most evaluated populations, including Asian, Latin American, Egyptian, and European cohorts (7,8,18–31). In contrast, the *CYP3A5**1/*1 genotype, corresponding to individuals with complete functional expression of the enzyme, shows variable distribution across populations and, in general, a lower frequency. However, it reaches high values in some specific groups, such as South Africa and Myanmar (7,8,18–31).

Nevertheless, in Latin American populations, the frequency of these genotypes may vary considerably within the same population. For example, in the Brazilian population, differences have been described in the frequency of the *CYP3A5**3/*3 genotype according to ethnic self-identification and geographic region, with values ranging from 24% to 70% across the analyzed subgroups, reflecting the genetic heterogeneity characteristic of these populations (6). In contrast, the frequency of the *CYP3A5**1/*1 genotype is lower, with values ranging from 0% to 13%.

In Peru, information on *CYP3A5* is limited. A study conducted in 77 healthy adult individuals showed a higher frequency of the *CYP3A5**3/*3 genotype compared with *CYP3A5**1/*1 (75.3% vs. 1.3%) (33). These results differ from those observed in the analyzed population in the present study, which consisted of patients with advanced chronic kidney disease and kidney transplantation, in whom the *CYP3A5**3/*3 genotype was absent.

Differences in the frequencies of the *CYP3A5**3 and *CYP3A5**1 alleles and genotypes reported in previous studies and those described in the present study may be due to multiple factors, including sample size, clinical and sociodemographic characteristics of the included population, patient origin, and the analytical technique used.

Regarding molecular analysis, PCR-RFLP was used in this study to determine the genotypes evaluated, a technique that has been widely used in previous pharmacogenetic studies for the characterization of *CYP3A5* variants (7,18). Likewise, other methodologies, such as genotyping assays with specific probes, have also been used for the analysis of *CYP3A5* and

CYP3A4 polymorphisms in kidney transplant recipients (7,34). In turn, the available pharmacogenetic guidelines for tacrolimus and *CYP3A5* guide the clinical interpretation of the genotype when it is available, without recommending a specific molecular technique for its characterization (5).

In this context, the main methodological limitation does not lie in the use of PCR-RFLP, but rather in the fact that the results obtained were not verified using an independent method, such as sequencing or genotyping assays with specific probes, due to logistical and budgetary constraints. In addition, because the study corresponds to a project developed during the 2019–2020 period, no remaining biological samples or primary laboratory records, including representative photographs of electrophoresis gels, are currently available to allow the molecular procedure to be repeated under different conditions or additional experimental verification to be performed. Therefore, this methodological limitation should be considered when interpreting the findings.

Furthermore, the limited availability of additional clinical, therapeutic, and pharmacokinetic information prevented broader characterization of the included population and incorporation of variables such as absolute glomerular filtration rate, creatinine, history and duration of hemodialysis, immunosuppressive treatment received, tacrolimus dose, or tacrolimus trough concentrations, particularly in patients who underwent kidney transplantation. Consequently, it was not possible to evaluate associations between *CYP3A5* genotypes and clinical, therapeutic, or pharmacokinetic variables.

Finally, the study design did not include systematic and longitudinal collection of pharmacokinetic data specifically aimed at evaluating the response to tacrolimus. In addition, other genetic variants potentially related to tacrolimus pharmacokinetics, such as *CYP3A4**22, or their interaction with clinical factors, were not analyzed. These aspects have been incorporated into previous pharmacokinetic models in adult kidney transplant recipients (35) and should be addressed in future research. Taken together, these limitations restrict interpretation of the findings to a descriptive estimate of the allelic and genotypic frequencies of *CYP3A5* in the population evaluated.

As strengths of the study, it should be noted that this is the first approach to describing the frequencies of the *CYP3A5**3 and *CYP3A5**1 alleles in a Peruvian pediatric population. It also includes patients with advanced chronic kidney disease and kidney transplantation, thereby providing preliminary information in a clinical group of particular relevance for tacrolimus pharmacogenetics. Furthermore, the use of PCR-RFLP, together with the use of two different restriction enzymes (BseMII and DdeI), represents a methodological strategy aimed at strengthening the assignment of the genotypes evaluated. However, this procedure does not replace verification using an independent confirmatory method, such as sequencing or genotyping assays with specific probes.

CONCLUSION

In the study population, the *CYP3A5**1 allele was the most frequent. The *CYP3A5**3/*3 genotype, associated with the CYP3A5 non-expressor phenotype, was not observed, which differs substantially from the frequencies reported for this genotype in other populations worldwide. These findings highlight the importance of considering population genetic variability in tacrolimus pharmacogenetics. Nevertheless, the results should be confirmed in future studies with larger sample sizes and complementary molecular methods, such as sequencing or genotyping assays with specific probes, to strengthen the reliability of the findings.

Author contributions

MLCM: Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – review and editing. JOTR: Methodology, Validation, Writing – original draft. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare no relevant financial or non-financial conflicts of interest.

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Data availability

The data supporting the findings of this study are available upon request from the corresponding author.

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