J Prev Epidemiol. 2019;4(2):e18 Review

Journal of Preventive Epidemiology http jprevepi.com

Meta-analysis shows no association of CYP3A5*3 variant with acute renal rejection in kidney-transplant patients receiving tacrolimus-based immunotherapy

Samrat Rakshit[1], **Rajeev Lochan Khare**[2], **Bhaskar VKS Lakkakula**[1*]

[1]Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India
[2]Department of Medicine, Pt. Jawahar Lal Nehru Memorial Medical College, Raipur, India

Correspondence to:
Bhaskar VKS Lakkakula, Email: lvksbhaskar@gmail.com

Received: 11 November 2019
Accepted: 20 December 2019
ePublished: 27 December 2019

Keywords: Tacrolimus, CYP3A5, rs776746, acute renal rejection, meta-analysis

Abstract

Life expectancy of kidney-transplanted patients is very low due to many causes, but allograft rejection is the central issue in organ transplantation. Immunosuppressive agents such as tacrolimus can solve this problem by inhibiting calcineurin. Tacrolimus has a very low therapeutic index and showed extensive intra-patient and inter-patient variability. The current meta-analysis is investigating the association between CYP3A5*3 (rs776746) variant and acute renal rejection (ARR) in tacrolimus treated population. To retrieve data, papers published on this subject were collected from PubMed, Google Scholar and Embase databases. Odds ratios (ORs) at 95% confidence intervals (CIs) were estimated to evaluate the association between CYP3A5*3 variant and risk of ARR. The pooled OR and CIs were calculated using random effect model. Heterogeneity was determined through Cochrane Q test and I-square statistic. Between-study heterogeneity was assessed through sensitivity analysis. Funnel plots and Egger's test were performed to check publication bias. This meta-analysis included 27 papers comprising 790 ARR and 2981 no rejection subjects. No association between CYP3A5*3 and ARR risk was found in overall (Dominant model OR=1.25; 95% CI 0.96-1.64; *P*=0.097; I-square: 42%) or in subgroup ethnicities such as Asian (Dominant model OR=1.20; 95% CI 0.79-1.85; *P*=0.302; I-square: 53.4%) and Caucasian (Dominant model OR=1.15; 95% CI 0.89-1.47; *P*=0.282; I-square: 33.7%) populations. There was no significant publication bias found in this meta-analysis. Based on current meta-analysis it can be concluded that there is no association between CYP3A5*3 variant and ARR in kidney-transplanted patients receiving tacrolimus-based immunotherapy.

Citation: Rakshit S, Khare RL, Lakkakula BVKS. Meta-analysis shows no association of CYP3A5*3 variant with acute renal rejection in kidney-transplant patients receiving tacrolimus-based immunotherapy. J Prev Epidemiol. 2019;4(2):e18.

Introduction

Kidney is one of the most vital organs of the body. It works as a blood purifier by eliminating toxic molecule through urine by glomerular filtration. Any alteration in the filtration by drug or disease may cause kidney injury. Acute renal failure or acute kidney injury (AKI) is a clinical syndrome characterized by the rapid loss of the kidney's excretory function (1). Incidence of AKI greatly varies between populations due to variety in geographical settings. In developing countries hypovolemia and diarrhea and in developed countries open-heart surgery is the common cause for the development of AKI (2). Over time, incidence of AKI has increase (3). AKI is very common in hospitalized patients; approximately half of the elderly ICU patients develop AKI (4). Kidney failure or end-stage renal disease (ESRD) is traditionally regarded as the most serious outcome of chronic kidney disease (CKD). In developed countries, CKD is often associated with old age, diabetes, hypertension, obesity, and cardiovascular disease, with diabetic glomerulosclerosis and hypertensive nephrosclerosis as the presumed pathological entities (5, 6). In Asia and sub-Saharan Africa, glomerulonephritis, herbal medication by rural people and antiretroviral therapies have contributed in the formation of CKD (7).

Kidney transplantation is a surgical procedure to place a healthy kidney into a patient with end-stage kidney disease. Compared to general population, life expectancy in patients undergoing kidney transplantation is lower. As allograft rejection becomes the central issue in organ transplantation, successful allograft function is needed (8). Immunosuppressive agents are best for induction, maintenance, and reversal of established rejection by inhibiting calcineurin. Tacrolimus is one of calcineurin inhibitors that improved short-term patient and graft outcomes by decreasing the incidence of rejection (9). Tacrolimus has a very low therapeutic index and showed

Core tip

Kidney transplantation is a surgical procedure to place a healthy kidney into a patient with end-stage kidney disease. Acute renal allograft rejection is the major issue in kidney transplantation. Tacrolimus is the primary immunosuppressant used in kidney transplant patients. Several studies have investigated the influence of CYP3A5 genetic polymorphism on tacrolimus daily dose requirements and acute rejection in kidney transplant patients. Our meta-analysis of CYP3A5*3 studies indicated that this polymorphism is not associated with the allograft rejection.

extensive intra-patient and inter-patient variability (10). Tacrolimus is metabolized by CYP3A, expected to express in all individuals. Genetic polymorphisms in CYP3A5 gene (CYP3A5*3) influence the tacrolimus trough blood levels. CYP3A5*3 is a common transition in intron 3 of the CYP3A5 gene, which introduces a frame shift during translation and results in truncated nonfunctional protein (11). The studies related to the association of CYP3A5*3 with ARR in kidney-transplanted patients receiving tacrolimus-based immunotherapy are inconclusive. Hence, we performed a meta-analysis to investigate the role of CYP3A5*3 and allograft rejection in renal transplant recipients.

Methods

Search strategy

To identify studies addressing the association between CYP3A5*3 polymorphism and risk of acute rejection in population treated with tacrolimus after renal transplantation, a comprehensive literature search was performed in PubMed, Google scholar and Embase. The following keywords were used to search literature: kidney transplantation, renal transplant, acute renal rejection, tacrolimus, CYP3A5*3, and rs776746. Further, references were manually reviewed to identify potentially relevant articles.

Study selection

Relevant studies were included in our meta-analysis only when they met the following criteria. The inclusion criteria were as follows: (1) studies included the effect of CYP3A5*3 genetic polymorphism on adult renal transplant recipients treated with tacrolimus; (2) studies having CYP3A5*3 genotypes information for both acute rejection and no rejection patients. Studies were excluded from meta-analysis if (1) article published in language other than English; (2) article without acute rejection and no rejection patients data as well as genotypes. Patients received tacrolimus for at least six months were considered for the study.

Data extraction and quality assessment

Based on the inclusion and exclusion criteria stated above, two authors independently evaluated every study for inclusion. The following information such as first author, year of publication, ethnicity; CYP3A5*3 genotypes of patients with acute rejection and no rejection were extracted from the selected papers (12-38).

Statistical analysis

To evaluate the strength of the relationship between genotypes and allograft rejection events after tacrolimus treatment, individual as well as pooled OR with 95% confidence intervals (95% CIs) were calculated. $P<0.05$ was considered significant. Statistical heterogeneity among all included studies was calculated by Q-statistic and I-square value. In case of significant heterogenicity, individual study effects were pooled using a random effects model otherwise fixed effects model was employed. To know the source of heterogeneity sensitivity analysis and subgroup analysis by ethnicity (Asians and Caucasians) was performed. As most of the studies have not given all genotypes were separately in allograft rejection groups and no rejection groups, we could not analyse the Hardy-Weinberg proportions and genetic association was tested only under dominant model (*1/*1+*1/*3 vs. *3/*3). Meta-analysis for the study was performed using MetaGenyo web tool (39).

Results

Study characteristics

Figure 1 represent search strategy, eligibility and included studies for current meta-analyses. As of May 2020, total 93 records were identified in different database after rigorous searching by both the author. Duplicate records (n = 37) were immediately removed after confirmation. After thorough screening of all the records, we found 14 such records that involved either other SNPs or a different drug were excluded. Upon full paper screening, some records that have incomplete information about genotype frequencies of patients were excluded (n = 10). After exclusion, we considered total 32 records suitable

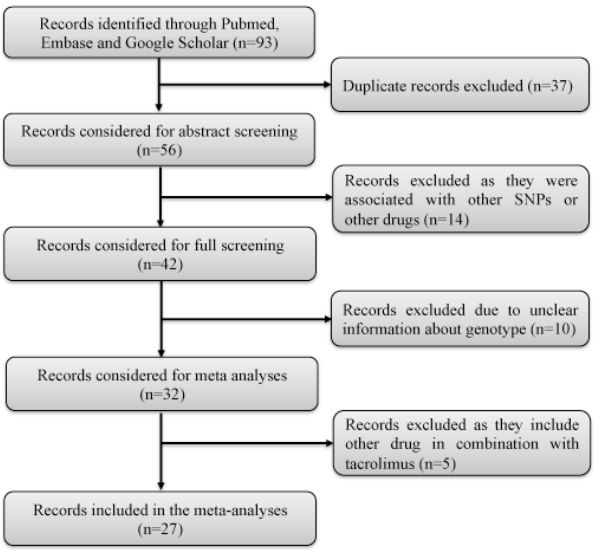

Figure 1. Flow Chart of Study Selection.

for meta-analyses. Out of 32 records, 5 records that used other drug combination with tacrolimus were eliminated from the meta-analysis. Finally, 27 records comprising 790 cases (allograft rejection) and 2981 controls (no rejection) were considered for the meta-analyses. The CYP3A5 gene expressor (*1/*1+*1/*3) and non-expressor (*3/*3) genotypes were presented in Table 1.

Association study

Forest plot of each individual studies as well as pooled studies (n = 27) involving association of CYP3A5*3 and ARR after tacrolimus treatment were presented in Figure 2. No association between CYP3A5*3 and ARR risk was found in overall (Dominant model OR = 1.25; 95% CI 0.96-1.64; $P = 0.097$; I^2: 42%) or in subgroup ethnicities such as Asian (Dominant model OR = 1.20; 95% CI 0.79-1.85; $P = 0.302$; I^2: 53.4%) and Caucasian (Dominant model OR = 1.15; 95% CI 0.89-1.47; $P = 0.282$; I^2: 33.7%) populations (Table 2).

Sensitivity analysis and publication bias

According to the I^2 value (41.8%), there is substantial heterogeneity between studies. We employed sensitivity analysis to confirm robustness of our study. Each time by omitting an independent study we did pooled analysis. We did not find any substantial difference in the pooled ORs (Figure 3). Begg's funnel plot showed symmetry in the shape indicating no publication bias (Figure 4), which was further confirmed by Egger's test (Dominant model, $P = 0.221$).

Discussion

The results of the present meta-analysis did not support the hypothesis that specific genotypes at the CYP3A5*3 loci modestly increase the risk of allograft rejection in kidney-transplant patients receiving tacrolimus-based immunotherapy. The current meta-analysis was free from any publication bias with significant between-study heterogeneity.

The CYP3A activity of an individual is the sum activity of the family of CYP3A genes, including CYP3A5 that represents at least 50% of the total hepatic CYP3A content. Higher CYP3A5 expression (between 21 and 204 pmol/mg protein) is determined by the presence of at least one CYP3A5*1 allele. Individuals homozygous for *CYP3A5 *3* shows reduced levels of intestinal or hepatic CYP3A5 (<21

Table 1. The distribution of CYP3A5 gene expressor and non-expressor genotypes in renal allograft recipients undergoing tacrolimus-based immunosuppression

Reference	Country	Ethnicity	Genotyping	Rejected allografts		Non-rejecting allografts	
				CYP3A5 Expressor	CYP3A5 Non-expressor	CYP3A5 Expressor	CYP3A5 Non-expressor
Hesselink et al (12)	Netherlands	Caucasian	PCR-RFLP	4	9	13	36
MacPhee et al (13)	UK	Caucasian	PCR-RFLP	7	43	8	60
Roy et al (14)	Canada	Caucasian	PCR-RFLP	3	8	6	27
Tirelli et al (15)	Italy	Caucasian	DNA Sequencing	4	3	3	16
Ferraresso et al (16)	Italy	Caucasian	DNA Sequencing	5	5	3	16
Hesselink et al (17)	Switzerland	Caucasian	PCR-RFLP	2	18	24	93
Quteineh et al (18)	France	Caucasian	TaqMan Genotyping	7	9	27	93
Singh et al (19)	India	Asian	PCR-RFLP	17	10	19	27
Satoh et al (20)	Japan	Asian	PCR-RFLP	3	8	16	14
Chen et al (21)	China	Asian	PCR-RFLP	9	2	29	27
Kuypers et al (22)	Belgium	Caucasian	PCR-RFLP	11	23	41	229
Min et al (23)	Korea	Asian	TaqMan Genotyping	21	17	8	16
Wang et al (24)	America	Caucasian	DNA Sequencing	3	11	36	58
Glowacki et al (25)	France	Caucasian	TaqMan Genotyping	5	17	32	149
Santoro et al (26)	Brazil	Caucasian	PCR-RFLP	7	8	55	83
Cho et al (27)	Korea	Asian	TaqMan Genotyping	4	4	22	40
Gervasini et al (28)	Spain	Caucasian	PCR-RFLP	1	15	9	78
Ro et al (29)	Korea	Asian	TaqMan Genotyping	21	30	90	108
Li et al (30)	China	Asian	SNaPshot assay	33	37	91	79
Cheng et al (31)	China	Asian	TaqMan Genotyping	3	2	21	9
Yaowakulpatana et al (32)	Thailand	Asian	TaqMan Genotyping	5	6	78	75
Flahault et al (33)	France	Caucasian	TaqMan Genotyping	55	95	177	250
Niioka et al (34)	Japan	Asian	PCR-RFLP	43	42	54	81
Lloberas et al (35)	Spain	Caucasian	TaqMan Genotyping	5	32	37	191
Gervasini et al (36)	Spain	Caucasian	TaqMan Genotyping	3	16	13	105
Udomkarnjananun et al (37)	Thailand	Asian	TaqMan Genotyping	8	9	23	7
Fernando et al (38)	India	Asian	HRM genotyping	18	4	42	37

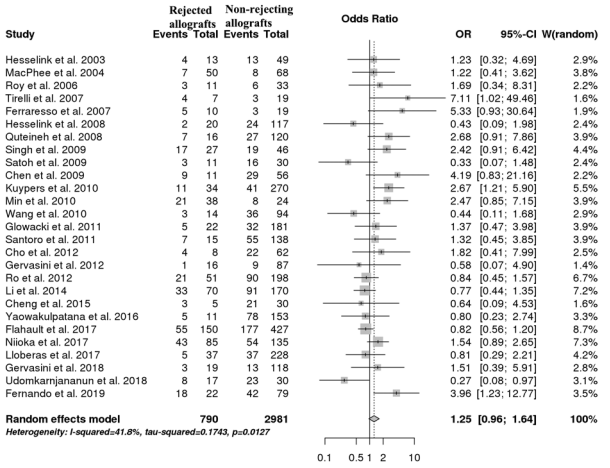

Figure 2. Forest plot depicting the association between CYP3A5*3 polymorphism and allograft outcome.

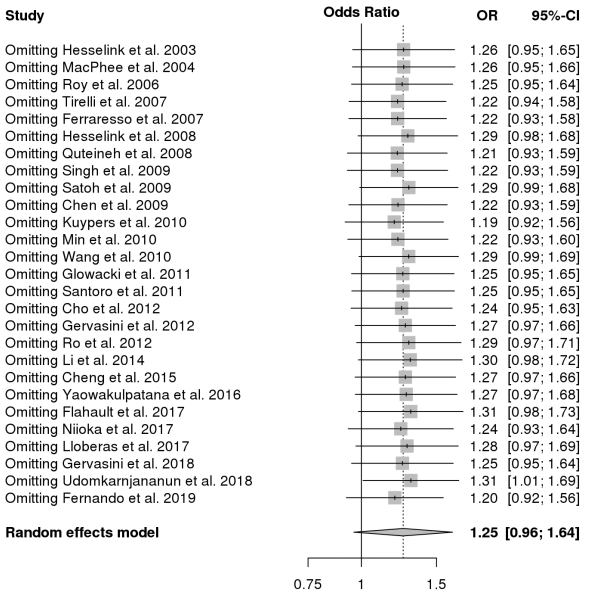

Figure 3. Forest plot for the sensitivity analysis in the meta-analysis

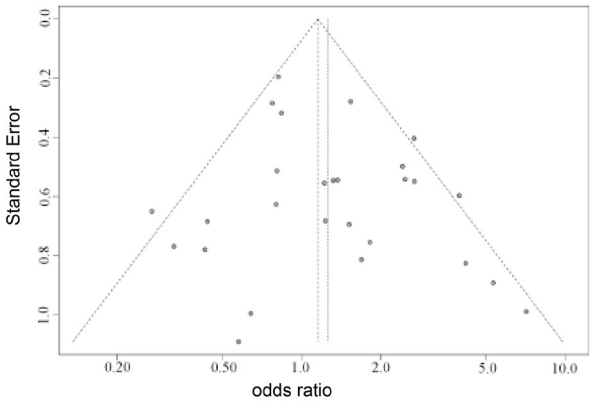

Figure 4. Begg's funnel plot depicting publication bias.

pmol/mg protein) (11). Hence polymorphisms in CYP3A5 may be the most important genetic contributor to inter-individual variations in CYP3A-dependent drug clearance. Kidney transplant patients with CYP3A5 polymorphism showed a modulated tacrolimus concentration/dose ratio, which severely affects nephrotoxicity. It was reported that CYP3A5 nonexpressor genotype (CYP3A5 ***3**/*3) exhibited significant lower dose requirement than CYP3A5 expressers (CYP3A5 ***1**/*1 or ***1**/*3) after transplantation as those patients require higher doses to achieve target blood concentrations (40). This clearly suggests that the recipient's genotypes are responsible for tacrolimus metabolism after transplantation. Further, the CYP3A5 expresser genotypes in transplant recipient patients treated with tacrolimus have a higher risk of acute rejection (15, 22, 38). However, majority of studies did not demonstrate this increased risk of acute rejection in individuals carrying CYP3A5 expressor genotypes (12,28-36).

Results of our meta-analysis are consistent with one of the previous meta-analyses in which the CYP3A5 polymorphisms had no effect on the acute rejection rates in renal transplant patients undergoing tacrolimus therapy (41). In contrast to this, a subsequent meta-analysis demonstrated that the expresser genotypes increase risk of acute rejection and tacrolimus-related nephrotoxicity (42). The dissimilarity in the results could be due to variation in the CYP3A5 expressor allele frequency ranging from 0.14 among sub-Saharan Africans to >0.95 in European populations (43-45). This meta-analysis showed significant level of unexplained heterogeneity that might

Table 2. Meta-analysis of the association of CYP3A5*3 polymorphism on allograft outcome

Dominant Model (*1/*1+*1/*3 vs. *3/*3)		Overall	Ethnicity	
			Caucasian	Asian
Number of studies		27	12	15
Test of heterogeneity	I^2%	41.8	33.7	53.4
	P value	0.013	0.099	0.015
Test of association	Model	Random effect	Fixed effect	Random effect
	OR (95% CI)	1.25 (0.96-1.64)	1.15 (0.89-1.47)	1.20 (0.79-1.85)
	P value	0.097	0.282	0.302
Publication bias	Egger's test *P* value	0.221	0.170	0.784

have aroused due to variations in the criteria adopted for determination of the incidence of acute rejection in the independent studies.

In summary, this meta-analysis revealed that the CYP3A5 expressers (CYP3A5*1/*1 or *1/*3) genotypes are not associated with a higher risk of tacrolimus-related acute renal rejection. Further research considering the donor-recipient genotypes is still needed to investigate the clinical and biological implications of this association.

Authors' contribution

Study conceived; BVKSL. Data collected; BVKSL, RLK and SR. Data analyzed; BVKSL, RLK and SR. Wrote the paper; BVKSL, RLK and SR. All authors have seen and approved the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

References

1. Duzova A, Bakkaloglu A, Kalyoncu M, Poyrazoglu H, Delibas A, Ozkaya O, et al. Etiology and outcome of acute kidney injury in children. Pediatr Nephrol. 2010;25:1453-61. doi:10.1007/s00467-010-1541-y.
2. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380:756-66. doi:10.1016/s0140-6736(11)61454-2.
3. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442-8. doi:10.1038/ki.2011.379.
4. Jiang L, Zhu Y, Luo X, Wen Y, Du B, Wang M, et al. Epidemiology of acute kidney injury in intensive care units in Beijing: the multi-center BAKIT study. BMC Nephrol. 2019;20:468-. doi:10.1186/s12882-019-1660-z.
5. Bhaskar LV, Mahin S, Ginila RT, Soundararajan P. Role of the ACE ID and PPARG P12A Polymorphisms in Genetic Susceptibility of Diabetic Nephropathy in a South Indian Population. Nephrourol Mon. 2013;5(3):813-7. doi:10.5812/numonthly.9573.
6. Ramanathan G, Ghosh S, Elumalai R, Periyasamy S, Lakkakula BVKS. Influence of angiotensin converting enzyme (ACE) gene rs4362 polymorphism on the progression of kidney failure in patients with autosomal dominant polycystic kidney disease (ADPKD). The Indian journal of medical research. 2016;143:748-55. doi:10.4103/0971-5916.191992.
7. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389:1238-52.
8. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351:2715-29. doi:10.1056/NEJMra033540.
9. Marcén R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs. 2009;69:2227-43. doi:10.2165/11319260-000000000-00000.
10. Cassuto E, Pageaux GP, Cantarovich D, Rostaing L, Loupy A, Roche B, et al. Adherence to and Acceptance of Once-Daily Tacrolimus After Kidney and Liver Transplant: Results From OSIRIS, a French Observational Study. Transplantation. 2016;100:2099-106. doi:10.1097/tp.0000000000001307.
11. Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet. 2001;27:383-91. doi:10.1038/86882.
12. Hesselink DA, van Schaik RH, van der Heiden IP, van der Werf M, Gregoor PJ, Lindemans J, et al. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther. 2003;74:245-54. doi:10.1016/s0009-9236(03)00168-1.
13. MacPhee IA, Fredericks S, Tai T, Syrris P, Carter ND, Johnston A, et al. The influence of pharmacogenetics on the time to achieve target tacrolimus concentrations after kidney transplantation. Am J Transplant. 2004;4:914-9. doi:10.1111/j.1600-6143.2004.00435.x.
14. Roy JN, Barama A, Poirier C, Vinet B, Roger M. Cyp3A4, Cyp3A5, and MDR-1 genetic influences on tacrolimus pharmacokinetics in renal transplant recipients. 2006;16:659-65. doi:10.1097/01.fpc.0000220571.20961.dd.
15. Tirelli S, Ferraresso M, Ghio L, Meregalli E, Martina V, Belingheri M, et al. The effect of CYP3A5 polymorphisms on the pharmacokinetics of tacrolimus in adolescent kidney transplant recipients. Med Sci Monit. 2008;14:Cr251-4.
16. Ferraresso M, Tirelli A, Ghio L, Grillo P, Martina V, Torresani E, et al. Influence of the CYP3A5 genotype on tacrolimus pharmacokinetics and pharmacodynamics in young kidney transplant recipients. Pediatr Transplant. 2007;11:296-300. doi:10.1111/j.1399-3046.2006.00662.x.
17. Hesselink DA, van Schaik RH, van Agteren M, de Fijter JW, Hartmann A, Zeier M, et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenet Genomics. 2008;18:339-48. doi:10.1097/FPC.0b013e3282f75f88.
18. Quteineh L, Verstuyft C, Furlan V, Durrbach A, Letierce A, Ferlicot S, et al. Influence of CYP3A5 genetic polymorphism on tacrolimus daily dose requirements and acute rejection in renal graft recipients. Basic Clin Pharmacol Toxicol. 2008;103:546-52. doi:10.1111/j.1742-7843.2008.00327.x.
19. Singh R, Srivastava A, Kapoor R, R KS, R DM. Impact of CYP3A5 and CYP3A4 gene polymorphisms on dose requirement of calcineurin inhibitors, cyclosporine and tacrolimus, in renal allograft recipients of North India. Naunyn Schmiedebergs Arch Pharmacol. 2009;380:169-77. doi:10.1007/s00210-009-0415-y.
20. Satoh S, Saito M, Inoue T, Kagaya H, Miura M, Inoue K, et al. CYP3A5 *1 allele associated with tacrolimus trough concentrations but not subclinical acute rejection or chronic allograft nephropathy in Japanese renal transplant recipients. Eur J Clin Pharmacol. 2009;65:473-81. doi:10.1007/s00228-008-0606-3.
21. Chen JS, Li LS, Cheng DR, Ji SM, Sun QQ, Cheng Z, et al. Effect of CYP3A5 genotype on renal allograft recipients treated with tacrolimus. Transplant Proc. 2009;41:1557-61. doi:10.1016/j.transproceed.2009.01.097.
22. Kuypers DR, Naesens M, de Jonge H, Lerut E, Verbeke K, Vanrenterghem Y. Tacrolimus dose requirements and CYP3A5 genotype and the development of calcineurin inhibitor-associated nephrotoxicity in renal allograft recipients. Ther Drug Monit. 2010;32:394-404. doi:10.1097/FTD.0b013e3181e06818.
23. Min SI, Kim SY, Ahn SH, Min SK, Kim SH, Kim YS, et al. CYP3A5 *1 allele: impacts on early acute rejection and graft function in tacrolimus-based renal transplant recipients. Transplantation. 2010;90:1394-400. doi:10.1097/TP.0b013e3181fa93a4.
24. Wang P, Mao Y, Razo J, Zhou X, Wong ST, Patel S, et al. Using

genetic and clinical factors to predict tacrolimus dose in renal transplant recipients. Pharmacogenomics. 2010;11:1389-402. doi:10.2217/pgs.10.105.
25. Glowacki F, Lionet A, Buob D, Labalette M, Allorge D, Provot F, et al. CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation. Nephrol Dial Transplant. 2011;26:3046-50. doi:10.1093/ndt/gfr253.
26. Santoro A, Felipe CR, Tedesco-Silva H, Medina-Pestana JO, Struchiner CJ, Ojopi EB, et al. Pharmacogenetics of calcineurin inhibitors in Brazilian renal transplant patients. Pharmacogenomics. 2011;12:1293-303. doi:10.2217/pgs.11.70.
27. Cho JH, Yoon YD, Park JY, Song EJ, Choi JY, Yoon SH, et al. Impact of cytochrome P450 3A and ATP-binding cassette subfamily B member 1 polymorphisms on tacrolimus dose-adjusted trough concentrations among Korean renal transplant recipients. Transplant Proc. 2012;44:109-14. doi:10.1016/j.transproceed.2011.11.004.
28. Gervasini G, Garcia M, Macias RM, Cubero JJ, Caravaca F, Benitez J. Impact of genetic polymorphisms on tacrolimus pharmacokinetics and the clinical outcome of renal transplantation. Transpl Int. 2012;25:471-80. doi:10.1111/j.1432-2277.2012.01446.x.
29. Ro H, Min S-I, Yang J, Moon KC, Kim YS, Kim SJ, et al. Impact of tacrolimus intraindividual variability and CYP3A5 genetic polymorphism on acute rejection in kidney transplantation. Ther Drug Monit. 2012;34:680-5. doi:10.1097/ftd.0b013e3182731809.
30. Li C-J, Li L, Lin L, Jiang H-X, Zhong Z-Y, Li W-M, et al. Impact of the CYP3A5, CYP3A4, COMT, IL-10 and POR genetic polymorphisms on tacrolimus metabolism in Chinese renal transplant recipients. PloS One. 2014;9(1):e86206-e. doi:10.1371/journal.pone.0086206.
31. Cheng Y, Li H, Meng Y, Liu H, Yang L, Xu T, et al. Effect of CYP3A5 polymorphism on the pharmacokinetics of tacrolimus and acute rejection in renal transplant recipients: experience at a single centre. Int J Clin Pract Suppl. 2015:16-22. doi:10.1111/ijcp.12662.
32. Yaowakulpatana K, Vadcharavivad S, Ingsathit A, Areepium N, Kantachuvesiri S, Phakdeekitcharoen B, et al. Impact of CYP3A5 polymorphism on trough concentrations and outcomes of tacrolimus minimization during the early period after kidney transplantation. Eur J Clin Pharmacol. 2016;72:277-83. doi:10.1007/s00228-015-1990-0.
33. Flahault A, Anglicheau D, Loriot MA, Thervet E, Pallet N. Clinical impact of the CYP3A5 6986A>G allelic variant on kidney transplantation outcomes. Pharmacogenomics. 2017;18:165-73. doi:10.2217/pgs-2016-0146.
34. Niioka T, Kagaya H, Saito M, Inoue T, Numakura K, Yamamoto R, et al. Impact of the CYP3A5 genotype on the distributions of dose-adjusted trough concentrations and incidence of rejection in Japanese renal transplant recipients receiving different tacrolimus formulations. Clin Exp Nephrol. 2017;21:787-96. doi:10.1007/s10157-016-1375-4.
35. Lloberas N, Elens L, Llaudó I, Padullés A, van Gelder T, Hesselink DA, et al. The combination of CYP3A4*22 and CYP3A5*3 single-nucleotide polymorphisms determines tacrolimus dose requirement after kidney transplantation. Pharmacogenet Genomics. 2017;27:313-22. doi:10.1097/fpc.0000000000000296.
36. Gervasini G, Garcia-Pino G, Vergara E, Mota-Zamorano S, Garcia-Cerrada M, Luna E. CYP3A genotypes of donors but not those of the patients increase the risk of acute rejection in renal transplant recipients on calcineurin inhibitors: a pilot study. Eur J Clin Pharmacol. 2018;74:53-60. doi:10.1007/s00228-017-2353-9.
37. Udomkarnjananun S, Townamchai N, Chariyavilaskul P, Iampenkhae K, Pongpirul K, Sirichindakul B, et al. The Cytochrome P450 3A5 Non-Expressor Kidney Allograft as a Risk Factor for Calcineurin Inhibitor Nephrotoxicity. Am J Nephrol. 2018;47:182-90. doi:10.1159/000487857.
38. Fernando ME, Sellappan M, Srinivasa Prasad ND, Suren S, Thirumalvalavan K. Influence of CYP3A5 and ABCB1 Polymorphism on Tacrolimus Drug Dosing in South Indian Renal Allograft Recipients. Indian J Nephrol. 2019;29:261-6. doi:10.4103/ijn.IJN_97_18.
39. Martorell-Marugan J, Toro-Dominguez D, Alarcon-Riquelme ME, Carmona-Saez P. MetaGenyo: a web tool for meta-analysis of genetic association studies. BMC Bioinformatics. 2017;18:563. doi:10.1186/s12859-017-1990-4.
40. Zong YP, Wang ZJ, Zhou WL, Zhou WM, Ma TL, Huang ZK, et al. Effects of CYP3A5 polymorphisms on tacrolimus pharmacokinetics in pediatric kidney transplantation: a systematic review and meta-analysis of observational studies. World J Pediatr. 2017;13:421-6. doi:10.1007/s12519-017-0035-4.
41. Terrazzino S, Quaglia M, Stratta P, Canonico PL, Genazzani AA. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics. 2012;22:642-5. doi:10.1097/FPC.0b013e3283557c74.
42. Rojas L, Neumann I, Herrero MJ, Boso V, Reig J, Poveda JL, et al. Effect of CYP3A5* 3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J. 2015;15:38-48. doi:10.1038/tpj.2014.38.
43. Bains RK, Kovacevic M, Plaster CA, Tarekegn A, Bekele E, Bradman NN, et al. Molecular diversity and population structure at the Cytochrome P450 3A5 gene in Africa. BMC Genet. 2013;14:34. doi:10.1186/1471-2156-14-34.
44. Suarez-Kurtz G, Vargens DD, Santoro AB, Hutz MH, de Moraes ME, Pena SDJ, et al. Global pharmacogenomics: distribution of CYP3A5 polymorphisms and phenotypes in the Brazilian population. PloS One. 2014;9:e83472-e. doi:10.1371/journal.pone.0083472.
45. Krasniqi V, Dimovski A, Bytyqi HQ, Eftimov A, Šimičević L, Božina N. Genetic polymorphisms of CYP2C9, CYP2C19, and CYP3A5 in Kosovar population. Arh Hig Rada Toksikol. 2017;68:180-4. doi:10.1515/aiht-2017-68-2998.