Published in final edited form as:

Curr Opin Nephrol Hypertens. 2014 November ; 23(6): 570–577. doi:10.1097/MNH.0000000000000065.

Role of Pharmacogenomics in Dialysis and Transplantation

Kelly Birdwell, MD, MSCI

Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN, United States

Abstract

Purpose of Review—Pharmacogenomics is the study of differences in drug response based on individual genetic background. With rapidly advancing genomic technologies and decreased costs of genotyping, the field of pharmacogenomics continues to develop. Application to patients with kidney disease provides growing opportunities for improving drug therapy.

Recent Findings—Pharmacogenomics studies are lacking in patients with chronic kidney disease and dialysis but are abundant in the kidney transplant field. A clinically actionable genetic variant exists in the *CYP3A5* gene, with the initial tacrolimus dose selection optimized based on *CYP3A5* genotype. Though many pharmacogenomics studies have focused on transplant immunosuppression pharmacokinetics, an expanding literature on pharmacodynamic outcomes like calcineurin inhibitor toxicity and new onset diabetes is providing new information on patients at risk.

Summary—Appropriately powered pharmacogenomics studies with well-defined phenotypes are needed to validate existing studies and unearth new findings in patients with kidney disease, especially the chronic kidney disease and dialysis population.

Keywords

pharmacogenetics; kidney; transplant; pharmacokinetics; pharmacodynamics

Introduction

Pharmacogenomics provides insight into the inter-individual variability in drug response based on one's genetic background. The term pharmacogenetics is used to describe a single variation, or polymorphism, in the genome and how this affects drug response. When multiple genetic variants or even the entire human genome are considered, as has been made possible with our current advanced technologies, the term pharmacogenomics is used. Increasingly more complex scenarios in drug response are being considered, including combinations of genetic variants or gene-gene interactions, the influence of the microbiome, and epigenetics.

Author of correspondence: Kelly Birdwell, MD, MSCI, Vanderbilt University Medical Center, Division of Nephrology and Hypertension, 1161 21st Avenue, S-3223 MCN, Nashville, TN 37232-2372, United States, Phone: +1 615 322 6976, Fax: +1 615 343 2605, kelly.birdwell@vanderbilt.edu.

Conflict of Interest: None

An obvious application of pharmacogenomics is to avoid serious adverse drug reactions. Additional goals include selecting the best drug when choices are available, optimal dose of a drug, and cost-savings for ineffective or potentially harmful therapy. Identifying genetic variation in drug response also may shed light on new targets for drug development.

Intense research in pharmacogenomics has been undertaken in certain fields (1), but less has been done in patients with kidney disease, with the exception of transplant. Additionally, pharmacogenetic studies of commonly used drugs often exclude patients with significant kidney disease, even though patients with kidney disease have a high burden of medical comorbidities that leads to many drug exposures. This review will provide the pertinent background and update of the most recent pharmacogenomics studies relevant to patients with kidney disease, while highlighting the needs for future research.

General pharmacogenomics principles

When prescribing a drug to a patient, many factors are considered that affect drug response, including patient age, sex, comorbid diseases, other medications, dietary supplements, and nutritional status. Pharmacogenomics incorporates another valuable factor by considering an individual's genetic background. While a single variation in an individual's genome may have a relatively large effect on drug response, in many cases multiple variants with small effects may contribute a large cumulative effect. One challenge of pharmacogenomics has been the ability to measure these multiple variants to explain an observed drug response, often because study cohorts are underpowered.

Genetic variation can affect both pharmacokinetics and pharmacodynamics of a drug, and these outcomes are used as the phenotypes in pharmacogenomics. Pharmacokinetics refers to actions of the body on a drug, including absorption, distribution, metabolism, and excretion (ADME) of an administered drug that are carried out by proteins like membrane transporters and metabolizing enzymes, including the cytochrome P450 system. Common pharmacokinetic phenotypes include drug concentration, dose, clearance, and area under the curve. Pharmacodynamics is action of a drug on the body and includes the intended drug binding target as well as unintended targets that may cause unwanted side effects.

When studying genetic variation, one may take a hypothesis-driven approach, where one or more candidate genes are selected based on known or suspected pharmacokinetic or pharmacodynamic mechanisms. But, with high throughput genomic technologies, a hypothesis-free discovery approach is used in which large numbers of genetic variants (thousands to millions) are examined simultaneously for a chosen drug phenotype, like for genome-wide association studies (GWAS) or whole exome sequencing studies. Important considerations in pharmacogenomics studies include: 1) accounting for ethnic background, since frequency of genetic variants vary by race; 2) study power, as many are underpowered especially with multiple comparisons adjustments for genomics studies; 3) definition of the phenotype of interest, which can vary widely from study to study making comparisons difficult; and, 4) presence of validation studies.

Pharmacogenomics of dialysis and chronic kidney disease

To date, pharmacogenomics has not been intensely applied to chronic kidney disease (CKD) and dialysis patients. While recent genomic studies of these populations exist, they are centered on kidney disease risk or progression, associated dialysis complications like arteriovenous fistula failure, or patient survival (2–4) rather than phenotypes related to drug response. But, a few potentially important pharmacogenomics associations have been explored. Notable are the renin-angiotensin system (RAS) blocker drugs, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), first line agents for the treatment of high blood pressure in CKD. Several genetic variants in RAS have been described, including the well-studied angiotensin converting enzyme insertion deletion (*ACE I/D*, rs4646994) that affects ACE levels. Early pharmacogenetic studies supported an effect of *ACE I/D* genotype on blood pressure response in patients taking ACEI and ARBs, though later studies have not, as recently reviewed (5). As RAS polymorphisms have not been consistently associated with antihypertensive response, currently no indication for clinical implementation exists (6).

A potential area of application would be pharmacogenomics of immunosuppression for glomerulonephritis (GN) based on several studies in kidney transplantation. Such studies should be repeated in the GN populations given other confounding factors exist, including lack of co-therapy with calcineurin inhibitors and differences in kidney function. For example, in a study of 39 patients with GN from lupus nephritis or ANCA-associated vasculitis taking mycophenolate, *UGT2B7*, *UGT1A*, and *ABCB1* genotypes were not associated with mycophenolate pharmacokinetics (7) as has been reported in kidney transplant (8).

Clearly the field is wide open for exploration in CKD and dialysis. Looking at extreme phenotypes, like dialysis patients who do and do not respond to erythropoietin, may be a good starting place, as it would be reasonable to think genetic variation in drug response might explain some of the variability. For example, Derebail et al. recently described presence of hemoglobinopathy and need for higher erythropoietin dose requirement in African Americans on dialysis (9). Pharmacogenomics studies admittedly are complex in this patient population with many confounders, including drug interactions and change in pharmacokinetics with renal failure. To date, there does not appear to be any specific drug recommendations to be made for CKD and dialysis patients based on pharmacogenomics studies.

Pharmacogenomics of kidney transplant

Modern immunosuppressive therapy for kidney transplantation, including calcineurin inhibitors, mycophenolate, mammalian target of rapamycin (mTOR) inhibitors, with or without steroids has allowed graft survival rates of 97% and acute rejection incidence of less than 10% at one year (10). Clinical use of these drugs, however, has been complicated by their narrow therapeutic index, where underexposure may increase acute rejection risk and overexposure may lead to toxicity (11). Often large pharmacokinetic inter-individual variability is noted. As a result, therapeutic drug monitoring is routinely used, with dose

adjustments based on blood concentrations (11). Though clearly useful, therapeutic drug monitoring limitations include unavailability for some drugs and inability to use for optimal starting dose. Furthermore, even when target drug concentrations are achieved, levels do not directly correlate with efficacy or toxicity. This was recently described by Bouamar et al., who did not find an association between tacrolimus trough blood concentrations and acute rejection incidence during 6 months post kidney transplant (12). This may be partially explained by the fact that whole blood concentrations do not accurately reflect important pharmacodynamics effects of a drug, for example intracellular lymphocyte concentrations for an immunosuppressive medication. Given these multiple caveats, investigators have used pharmacogenomics approaches in hopes of better understanding and using transplant immunosuppression, with the majority of studies focused on calcineurin inhibitors.

Calcineurin inhibitors and pharmacokinetic phenotypes

The calcineurin inhibitors cyclosporine and tacrolimus are substrates for the ABCB1 drug efflux transporter encoded by *ABCB1* gene and are metabolized by the cytochrome (CYP) P450 3A family enzymes, particularly CYP3A4 and CYP3A5. In the *CYP3A5* gene, a single nucleotide polymorphism (SNP) may occur (rs776746, 6986G>A) that affects CYP3A5 expression. In individuals with at least one *1 allele, functional CYP3A5 protein is present (CYP3A5 expressers), whereas those homozygous for *3 have no CYP3A5 expression (CYP3A5 non-expressers) (13). For tacrolimus, it has been well established through both candidate gene and larger genomic studies that CYP3A5 non-expressers have higher dose-adjusted trough blood concentrations and lower dose requirements than CYP3A5 expressers, with findings consistent across race groups and adult and pediatric kidney transplant recipients (14–19). Recent studies confirming this include a study of 177 kidney transplant recipients in Norway, 206 recipients from northern Spain, as well as a one of Korean recipients in which both tacrolimus and its metabolites were associated with *CYP3A5* status, among others (20–24). In addition to high inter-individual variability, some transplant recipients also have marked intra-individual variability with tacrolimus, which has been identified as a risk factor for nephrotoxicity. Recipient *CYP3A5* has not been associated with tacrolimus intra-individual variability in kidney transplant recipients (25), reinforced in a recent study of 118 kidney transplant recipients followed 1 year post transplant (26).

With 39% of tacrolimus inter-individual variability explained by *CYP3A5* (15) investigators have sought other contributing variants. Past studies have focused on the *ABCB1* polymorphisms, rs1045642 (3435C>T), rs2032582 (2677G>A/T), and rs1128503 (1236C>T), which are in linkage disequilibrium and inherited as a haplotype (13). Results of these SNPs on tacrolimus pharmacokinetics are conflicting and generally appear not be relevant when considered individually (23, 27). A recent study of 108 Brazilian kidney transplant recipients did show recipients homozygous for the T allele (TTT/TTT) at all 3 SNPs had higher dose-normalized trough blood concentrations than controls (CGC/CGC or CGC/TTT), even when stratified by *CYP3A5* status (28). Newer studied variants include *CYP3A4**22, *POR**28, and *PPARA*. In *CYP3A4**22(rs35599367, C>T), the T allele is associated with decreased tacrolimus dose requirement (23, 29). Elens et al. showed this effect was independent and additive when stratifying patients by *CYP3A5* status. However, others have been unable to confirm this finding (22, 30, 31). Another recently highlighted

variant, important in CYP-mediated drug oxidation, is *POR**28 (rs1057868, C>T), with the T allele associated with increased tacrolimus dose requirement. In these studies, *POR**28 was only relevant in patients who were also CYP3A5 expressers (21, 32–34). The gene *PPARA* encodes the peroxisome proliferator-activated receptor alpha (PPAR- α), and variants rs4253728, G>A and rs4823613, A>G affect CYP3A activity. Initial studies of *PPARA* and tacrolimus show conflicting results (21, 35). These newly described variants will need further validation across populations before deciding their clinical importance. In addition, further studies assessing the interaction among multiple genetic variants will be needed to realize the full potential of pharmacogenomics, such as the relevance of *POR**28 only in CYP3A5 expressers above. Please see Table 1 for a summary of variants related to transplant pharmacokinetics.

Despite the strong association of *CYP3A5* with tacrolimus pharmacokinetics, it remains unclear if dosing by genotype will improve transplant outcomes, especially since therapeutic drug monitoring allows quick adjustment of dose. Randomized controlled trials showing benefit are needed, but only one is completed. Thervet, et al. showed genotyped-guided dosing did achieve more kidney transplant recipients reaching target tacrolimus level by day 3 compared to controls, but no differences were seen in patient/graft survival, nephrotoxicity, or acute rejection over 3 months follow up (36). More studies like this are needed with longer duration of follow up and carefully phenotyped populations to see if certain sub groups benefit, like a high versus low risk group for acute rejection. In addition, validated dosing algorithms incorporating clinical and genetic factors that work across multiple cohorts are needed. This was exemplified by a published equation for tacrolimus dosing, which validated in one patient cohort but was not able to be validated in another (40–42). Lack of a universal algorithm probably reflects in part our lack of full understanding of factors that contribute to tacrolimus drug variability (43).

The impact of polymorphisms on cyclosporine pharmacokinetics has been less clear due to conflicting reports, as recently reviewed (13). A meta-analysis of *CYP3A5**3 in 1821 kidney transplant recipients concluded that *CYP3A5**3 may have a small effect on cyclosporine pharmacokinetics but is not likely clinically relevant (44). Likewise, a recent review of *ABCB1* determined a lack of consistent effect on cyclosporine pharmacokinetics, though it might be important in nephrotoxicity (discussed below) (27). Unlike for tacrolimus, *CYP3A4**22 has been consistently associated with higher dose-adjusted trough blood concentrations for cyclosporine, indicating need for lower dose (21, 29, 30). Cyclosporine treated patients who are CYP3A5 non-expressers and homozygous for *POR**28 may have higher CYP3A4 activity, leading to lower dose-adjusted trough blood concentrations and need for higher dose (32), but further confirmatory studies are needed. Based on studies to date, dosing of cyclosporine based on genetic variants is not warranted.

Calcineurin inhibitors and pharmacodynamic phenotypes

Blood drug concentrations may not directly correspond with pharmacodynamic outcomes, as observed clinically when a patient experiences acute rejection or toxicity despite drug levels being in therapeutic range. Thus pharmacogenetic study of pharmacodynamic outcomes in kidney transplant is of increasing interest, though overall less well studied. A summary of

these are in Table 2. Acute rejection is commonly investigated, but studies to date have not shown a strong association of pharmacogenes with acute rejection in kidney transplant recipients treated with calcineurin inhibitors, as lately reviewed (13, 44). A recent meta-analysis confirmed that *CYP3A5* and *ABCB1* have minimal effect on acute rejection in tacrolimus treated patients (24).

As a major contributor to chronic allograft failure, calcineurin inhibitor nephrotoxicity remains an important modifiable cause. Notably, blood levels may not reflect local accumulation of calcineurin inhibitors in renal tissue and risk of nephrotoxicity. For example, Zheng et al. showed that in healthy volunteer *CYP3A5* expressers and nonexpressers, cyclosporine oral clearance was similar, but *CYP3A5* expressers had 50% higher area under the concentration time curves of active cyclosporine metabolites, with decreased urinary clearance, suggesting increased intra-renal accumulation that could contribute to nephrotoxicity (50). Another study of cyclosporine treated kidney transplant recipients showed that even though cyclosporine blood levels were not associated with *ABCB1* polymorphisms, those homozygous for 3435TT had an increased odds of nephrotoxicity (OR 4.2, 95% CI 1.3–13.9) and gingival hyperplasia, again suggesting blood levels may not fully reflect exposure at target sites (51). Overall, however, pharmacogenetic studies of recipient *CYP3A5* and *ABCB1* in calcineurin inhibitor toxicity have shown mixed results, making it difficult to draw conclusions.

On the other hand, donor genotype may be important in nephrotoxicity. This review so far has focused on recipient genotype, but *CYP3A5* and *ABCB1* and other pharmacogenes are expressed in the kidney, so that the donor kidney genotype may differ from that of the recipient, affecting levels of calcineurin inhibitors at the target organ. A study of 4,471 white kidney transplant recipients on calcineurin inhibitors by Moore et al. showed an association of donor *ABCB1* 3435CC and increased long term graft failure, though this was in contrast to smaller studies that had shown the 3435TT genotype to be worse (46). Further pharmacogenomics studies considering donor-recipient genotypes are warranted (52).

New onset diabetes after transplantation (NODAT) is another toxicity observed with tacrolimus but also seen with cyclosporine and mTOR inhibitors. In addition to well established clinical factors like age, gender, and weight gain, genetics likely play a role with many variants recently described but not necessarily validated, reflecting small if real effects. One recent paper by McCaughan described 7 SNPs in genes related to β -cell apoptosis (48). Other recent studies have implicated *POR**28 and *PPARA* (47), adiponectin gene (rs1501299, 276G>T) (53), mitochondrial haplogroup H (54), and Fok1 vitamin D receptor polymorphisms. Many of the described variants have plausible biologic connections to glucose metabolism pathways and should be further studied to validate findings and explain the pathogenesis of NODAT (55).

Pharmacogenomics provides novel ways for monitoring drug efficacy. For example, Yoon and colleagues have showed that in monocytes from kidney transplant recipients homozygous for *CYP3A5**3, the HLA/DR+ mean fluorescent intensity was significantly lower compared to those from *CYP3A5**1 carriers, with significant negative correlations with dose-adjusted trough blood concentrations, suggesting the HLA/DR expression on

monocytes might be explored as a tool for monitoring of tacrolimus toxicity (56). In another study, Vafadari et al. showed the pharmacodynamic effect of tacrolimus on inhibiting IL-2 production depended on *ABCB1* 3435C>T genotype (57).

Other immunosuppressive drugs: mycophenolate and mTOR inhibitors

Mycophenolate mofetil (MMF) is a prodrug that is hydrolyzed to the active form mycophenolic acid (MPA). The pharmacokinetics of MPA are complex, including hepatic conjugation by uridine diphosphate glucuronosyl transferases (UGTs), producing active and inactive metabolites that may enter enterohepatic circulation. Most studies in kidney transplant recipients have focused on polymorphisms in the UGT isoforms, particularly in *UGT1A9* and *UGT2B7*, as well as genes encoding organic anion transporters (OATs), like *SLCO1B3*, which have been recently reviewed (8, 37). Several studies have reported *UGT1A9* SNPs (rs6714486, 275T>A and rs17868320, 2152C>T) are associated with lower MPA exposure though conflicting evidence exists. Interestingly, in some studies, the effect of UGT polymorphisms appears to depend on which calcineurin inhibitor is present (58). Genetic variation in the target of MPA, inosine 5-monophosphate dehydrogenase (IMPDH), has also been studied with some but not all studies showing association with acute rejection (8, 45). The commonly recognized toxicities of MPA including leukopenia, anemia, and diarrhea have been examined with mixed results (8, 59). In summary, though provocative, pharmacogenetic variants are not yet indicated for clinical implementation for mycophenolate.

The mTOR inhibitors sirolimus and everolimus have been the least studied drugs in transplant pharmacogenomics. Like the calcineurin inhibitors, they are substrates of the *ABCB1* drug efflux transporter and *CYP3A4/CYP3A5* enzymes (45). Several studies have shown that patients homozygous for *CYP3A5**3 have higher dose-adjusted sirolimus levels (38), but this has not been as widely validated as for tacrolimus. *CYP3A5**3 has not been associated with everolimus pharmacokinetics (30, 39). A common adverse effect of sirolimus therapy is hyperlipidemia, and one study group has shown an association of *ABCB1* 3435C>T with increased sirolimus blood levels as well as with higher total cholesterol and low-density lipoprotein level-C in kidney transplant recipients (49).

Conclusion

Pharmacogenomics has been limited in the CKD and dialysis population, whereas a growing wealth of information is available for kidney transplantation. The only actionable genetic variant to date appears to be the *CYP3A5* genotype for initial tacrolimus dosing in kidney transplant. But, the long term impact of adjusting tacrolimus dose based on *CYP3A5* genotype requires further study. Though pharmacogenomics in kidney disease has not proven to benefit clinical practice as quickly as once hoped, value exists in pushing ahead in this exciting field. Further studies assessing the interaction among multiple genetic variants will be needed to realize the full potential of pharmacogenomics. Some investigators have begun such inquiries, such as the relevance of *POR**28 only in *CYP3A5* expressers taking tacrolimus (32), while other efforts to combine genotypes have not improved results (30). For transplant, dual consideration of donor and recipient genotype is vital. As the focus

moves to donor-recipient gene interactions, gene-gene interactions, and gene-environment interactions in the setting of increasingly sophisticated genomic technologies and computational analysis, much is yet to be discovered and tested to improve our management of patients with kidney disease when it comes to drug therapy.

Acknowledgments

Kelly Birdwell currently has funding from the National Institutes of Health (1 K23 GM100183 from the National Institute of General Medical Sciences; Vanderbilt CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences and by Award Number S10RR027033 from the National Center for Research Resources).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Weeke P, Roden DM. Applied pharmacogenomics in cardiovascular medicine. Annual review of medicine. 2014; 65:81–94. Epub 2013/10/12.
2. Verschuren JJ, Ocak G, Dekker FW, et al. Candidate gene analysis of arteriovenous fistula failure in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(8):1358–66. Epub 2013/04/06. [PubMed: 23559680]
3. Ko GJ, Lee YM, Lee EA, et al. The association of Klotho gene polymorphism with the mortality of patients on maintenance dialysis. Clinical nephrology. 2013; 80(4):263–9. Epub 2013/09/03. [PubMed: 23993164]
4. Ocak G, Drechsler C, Vossen CY, et al. Single nucleotide variants in the protein C pathway and mortality in dialysis patients. PLoS One. 2014; 9(5):e97251. Epub 2014/05/13. [PubMed: 24816905]
5. Santos PC, Krieger JE, Pereira AC. Renin-angiotensin system, hypertension, and chronic kidney disease: pharmacogenetic implications. Journal of pharmacological sciences. 2012; 120(2):77–88. Epub 2012/10/20. [PubMed: 23079502]
6. Konoshita T. Do genetic variants of the Renin-Angiotensin system predict blood pressure response to Renin-Angiotensin system-blocking drugs?: a systematic review of pharmacogenomics in the Renin-Angiotensin system. Current hypertension reports. 2011; 13(5):356–61. Epub 2011/05/13. [PubMed: 21562941]
7. Sam WJ, Joy MS. Population pharmacokinetics of mycophenolic acid and metabolites in patients with glomerulonephritis. Ther Drug Monit. 2010; 32(5):594–605. Epub 2010/08/26. [PubMed: 20736896]
- *8. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. Archives of toxicology. 2014; 88(7):1351–89. Epub 2014/05/06. This is a comprehensive review on the pharmacokinetics and pharmacodynamics of mycophenolate as used for transplant, including the contribution of genetic variants. [PubMed: 24792322]
- *9. Derebail VK, Lacson EK Jr, Kshirsagar AV, et al. Sickle trait in African-American hemodialysis patients and higher erythropoiesis-stimulating agent dose. J Am Soc Nephrol. 2014; 25(4):819–26. Epub 2014/01/25. This study is a good example how a common clinically identifiable phenotype, like differences in erythropoietin response, can form the basis of a pharmacogenetic study. [PubMed: 24459231]
10. OPTN/SRTR. 2012 Annual Data Report [database on the Internet]. Department of Health and Human Services, Health resources and Services Administration; 2014.

11. Wallemacq P, Armstrong VW, Brunet M, et al. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. *Ther Drug Monit.* 2009; 31(2):139–52. Epub 2009/01/30. [PubMed: 19177031]
- *12. Bouamar R, Shuker N, Hesselink DA, et al. Tacrolimus predose concentrations do not predict the risk of acute rejection after renal transplantation: a pooled analysis from three randomized-controlled clinical trials. *Am J Transplant.* 2013; 13(5):1253–61. Epub 2013/03/14. This study importantly highlights how the commonly clinical practice of therapeutic drug monitoring to target certain drug levels may not be helpful in preventing acute rejection. [PubMed: 23480233]
13. Elens L, Bouamar R, Shuker N, et al. Clinical implementation of pharmacogenetics in kidney transplantation: calcineurin inhibitors in the starting blocks. *Br J Clin Pharmacol.* 2014; 77(4): 715–28. Epub 2013/10/15. [PubMed: 24118098]
- *14. Hesselink DA, Bouamar R, Elens L, et al. The role of pharmacogenetics in the disposition of and response to tacrolimus in solid organ transplantation. *Clin Pharmacokinet.* 2014; 53(2):123–39. Epub 2013/11/20. Excellent comprehensive review on pharmacogenetics of tacrolimus in transplantation. [PubMed: 24249597]
15. Birdwell KA, Grady B, Choi L, et al. The use of a DNA biobank linked to electronic medical records to characterize pharmacogenomic predictors of tacrolimus dose requirement in kidney transplant recipients. *Pharmacogenet Genomics.* 2012; 22(1):32–42. Epub 2011/11/24. [PubMed: 22108237]
16. Jacobson PA, Oetting WS, Brearley AM, et al. Novel Polymorphisms Associated With Tacrolimus Trough Concentrations: Results From a Multicenter Kidney Transplant Consortium. Transplantation. 2011 Epub 2011/01/06.
17. Hesselink DA, van Schaik RH, van der Heiden IP, 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(3):245–54. Epub 2003/09/11. [PubMed: 12966368]
18. Zhao W, Elie V, Roussey G, et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clin Pharmacol Ther.* 2009; 86(6): 609–18. Epub 2009/10/30. [PubMed: 19865079]
19. Macphee IA, Fredericks S, Mohamed M, et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. *Transplantation.* 2005; 79(4):499–502. Epub 2005/02/25. [PubMed: 15729180]
20. Yoon SH, Cho JH, Kwon O, et al. CYP3A and ABCB1 genetic polymorphisms on the pharmacokinetics and pharmacodynamics of tacrolimus and its metabolites (M-I and M-III). *Transplantation.* 2013; 95(6):828–34. Epub 2013/02/01. [PubMed: 23364483]
21. Lunde I, Bremer S, Midtvedt K, et al. The influence of CYP3A, PPARA, and POR genetic variants on the pharmacokinetics of tacrolimus and cyclosporine in renal transplant recipients. *European journal of clinical pharmacology.* 2014; 70(6):685–93. Epub 2014/03/25. [PubMed: 24658827]
22. Tavira B, Coto E, Diaz-Corte C, et al. A search for new CYP3A4 variants as determinants of tacrolimus dose requirements in renal-transplanted patients. *Pharmacogenet Genomics.* 2013; 23(8):445–8. Epub 2013/06/20. [PubMed: 23778326]
23. Kurzawski M, Dabrowska J, Dziewanowski K, et al. CYP3A5 and CYP3A4, but not ABCB1 polymorphisms affect tacrolimus dose-adjusted trough concentrations in kidney transplant recipients. *Pharmacogenomics.* 2014; 15(2):179–88. Epub 2014/01/22. [PubMed: 24444408]
24. Terrazzino S, Quaglia M, Stratta P, et al. 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(8):642–5. Epub 2012/07/13. [PubMed: 22786571]
25. Pashae N, Bouamar R, Hesselink DA, et al. CYP3A5 genotype is not related to the inpatient variability of tacrolimus clearance. *Ther Drug Monit.* 2011; 33(3):369–71. Epub 2011/05/14. [PubMed: 21566507]
26. Spierings N, Holt DW, MacPhee IA. CYP3A5 genotype had no impact on inpatient variability of tacrolimus clearance in renal transplant recipients. *Ther Drug Monit.* 2013; 35(3):328–31. Epub 2013/05/15. [PubMed: 23666583]

27. Shuker N, Bouamar R, Weimar W, et al. ATP-binding cassette transporters as pharmacogenetic biomarkers for kidney transplantation. *Clin Chim Acta*. 2012; 413(17–18):1326–37. Epub 2011/10/15. [PubMed: 21996082]
28. Cusinato DA, Lacchini R, Romao EA, et al. Relationship of Cyp3a5 Genotype and Abcb1 Diplo type to Tacrolimus Disposition in Brazilian Kidney Transplant Patients. *Br J Clin Pharmacol*. 2014 Epub 2014/02/18.
29. Elens L, van Schaik RH, Panin N, et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenomics*. 2011; 12(10):1383–96. Epub 2011/09/10. [PubMed: 21902502]
30. Moes DJ, Swen JJ, den Hartigh J, et al. Effect of CYP3A4*22, CYP3A5*3, and CYP3A Combined Genotypes on Cyclosporine, Everolimus, and Tacrolimus Pharmacokinetics in Renal Transplantation. *CPT: pharmacometrics & systems pharmacology*. 2014; 3:e100. Epub 2014/02/14. [PubMed: 24522145]
31. Santoro AB, Struchiner CJ, Felipe CR, et al. CYP3A5 genotype, but not CYP3A4*1b, CYP3A4*22, or hematocrit, predicts tacrolimus dose requirements in Brazilian renal transplant patients. *Clin Pharmacol Ther*. 2013; 94(2):201–2. Epub 2013/04/17. [PubMed: 23588314]
32. Elens L, Hesselink DA, Bouamar R, et al. Impact of POR*28 on the pharmacokinetics of tacrolimus and cyclosporine A in renal transplant patients. *Ther Drug Monit*. 2014; 36(1):71–9. Epub 2013/09/26. [PubMed: 24061445]
33. Zhang JJ, Zhang H, Ding XL, et al. Effect of the P450 oxidoreductase 28 polymorphism on the pharmacokinetics of tacrolimus in Chinese healthy male volunteers. *European journal of clinical pharmacology*. 2013; 69(4):807–12. Epub 2012/10/26. [PubMed: 23097010]
34. Gijzen VM, van Schaik RH, Soldin OP, et al. P450 oxidoreductase *28 (POR*28) and tacrolimus disposition in pediatric kidney transplant recipients—a pilot study. *Ther Drug Monit*. 2014; 36(2): 152–8. Epub 2013/10/04. [PubMed: 24089076]
35. Kurzwaski M, Malinowski D, Dziewanowski K, et al. Impact of PPARA and POR polymorphisms on tacrolimus pharmacokinetics and new-onset diabetes in kidney transplant recipients. *Pharmacogenet Genomics*. 2014 Epub 2014/06/13.
36. Thervet E, Lorient MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther*. 2010; 87(6):721–6. Epub 2010/04/16. [PubMed: 20393454]
37. Dupuis R, Yuen A, Innocenti F. The influence of UGT polymorphisms as biomarkers in solid organ transplantation. *Clin Chim Acta*. 2012; 413(17–18):1318–25. Epub 2012/02/14. [PubMed: 22327003]
38. Woillard JB, Kamar N, Coste S, et al. Effect of CYP3A4*22, POR*28, and PPARA rs4253728 on sirolimus in vitro metabolism and trough concentrations in kidney transplant recipients. *Clin Chem*. 2013; 59(12):1761–9. Epub 2013/08/27. [PubMed: 23974086]
39. Moes DJ, Press RR, den Hartigh J, et al. Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients. *Clin Pharmacokinet*. 2012; 51(7):467–80. Epub 2012/05/26. [PubMed: 22624503]
40. Passey C, Birnbaum AK, Brundage RC, et al. Dosing equation for tacrolimus using genetic variants and clinical factors. *Br J Clin Pharmacol*. 2011; 72(6):948–57. Epub 2011/06/16. [PubMed: 21671989]
41. Passey C, Birnbaum AK, Brundage RC, et al. Validation of tacrolimus equation to predict troughs using genetic and clinical factors. *Pharmacogenomics*. 2012; 13(10):1141–7. Epub 2012/08/23. [PubMed: 22909204]
42. Boughton O, Borgulya G, Cecconi M, et al. A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. *Br J Clin Pharmacol*. 2013 Epub 2013/01/12.
43. Elens L, Hesselink DA, van Schaik RH, et al. The CYP3A4*22 allele affects the predictive value of a pharmacogenetic algorithm predicting tacrolimus predose concentrations. *Br J Clin Pharmacol*. 2013; 75(6):1545–7. Epub 2012/11/21. [PubMed: 23163400]

44. Tang HL, Ma LL, Xie HG, et al. Effects of the CYP3A5*3 variant on cyclosporine exposure and acute rejection rate in renal transplant patients: a meta-analysis. *Pharmacogenet Genomics*. 2010; 20(9):525–31. Epub 2010/07/01. [PubMed: 20588203]
45. Murray B, Hawes E, Lee RA, et al. Genes and beans: pharmacogenomics of renal transplant. *Pharmacogenomics*. 2013; 14(7):783–98. Epub 2013/05/09. [PubMed: 23651025]
46. Moore J, McKnight AJ, Dohler B, et al. Donor ABCB1 variant associates with increased risk for kidney allograft failure. *J Am Soc Nephrol*. 2012; 23(11):1891–9. Epub 2012/10/16. [PubMed: 23064017]
47. Elens L, Sombogaard F, Hesselink DA, et al. Single-nucleotide polymorphisms in P450 oxidoreductase and peroxisome proliferator-activated receptor- α are associated with the development of new-onset diabetes after transplantation in kidney transplant recipients treated with tacrolimus. *Pharmacogenet Genomics*. 2013; 23(12):649–57. Epub 2013/10/12. [PubMed: 24113216]
- **48. McCaughan JA, McKnight AJ, Maxwell AP. Genetics of new-onset diabetes after transplantation. *J Am Soc Nephrol*. 2014; 25(5):1037–49. Epub 2013/12/07. This is a recent and first exploratory genome wide study of new onset diabetes after transplant, finding significantly associated genetic variants related to β -cell apoptosis, which is consistent with the suspected pathophysiology of β -cell dysfunction in new onset diabetes. [PubMed: 24309190]
49. Sam WJ, Chamberlain CE, Lee SJ, et al. Associations of ABCB1 and IL-10 genetic polymorphisms with sirolimus-induced dyslipidemia in renal transplant recipients. *Transplantation*. 2012; 94(9):971–7. Epub 2012/10/18. [PubMed: 23073467]
50. Zheng S, Tasnif Y, Hebert MF, et al. CYP3A5 gene variation influences cyclosporine A metabolite formation and renal cyclosporine disposition. *Transplantation*. 2013; 95(6):821–7. Epub 2013/01/29. [PubMed: 23354298]
51. Garcia M, Macias RM, Cubero JJ, et al. ABCB1 polymorphisms are associated with cyclosporine-induced nephrotoxicity and gingival hyperplasia in renal transplant recipients. *European journal of clinical pharmacology*. 2013; 69(3):385–93. Epub 2012/08/14. [PubMed: 22886152]
52. Brunet M, Millan O, Martorell J. Donor-recipient genetic diversity: the role of pharmacogenomics in kidney transplantation. *Pharmacogenomics*. 2013; 14(12):1369–72. Epub 2013/09/13. [PubMed: 24024888]
53. Nicoletto BB, Souza GC, Fonseca NK, et al. Association between 276G/T adiponectin gene polymorphism and new-onset diabetes after kidney transplantation. *Transplantation*. 2013; 96(12):1059–64. Epub 2013/08/30. [PubMed: 23985723]
54. Tavira B, Gomez J, Diaz-Corte C, et al. Mitochondrial DNA haplogroups and risk of new-onset diabetes among tacrolimus-treated renal transplanted patients. *Gene*. 2014; 538(1):195–8. Epub 2014/01/22. [PubMed: 24445060]
55. Yao B, Chen X, Shen FX, et al. The incidence of posttransplantation diabetes mellitus during follow-up in kidney transplant recipients and relationship to FokI vitamin D receptor polymorphism. *Transplant Proc*. 2013; 45(1):194–6. Epub 2013/02/05. [PubMed: 23375298]
56. Lee YJ, Kim B, Lee JE, et al. Randomized trial of cyclosporine and tacrolimus therapy with steroid withdrawal in living-donor renal transplantation: 5-year follow-up. *Transpl Int*. 2010; 23(2):147–54. Epub 2009/09/12. [PubMed: 19744223]
57. Vafadari R, Bouamar R, Hesselink DA, et al. Genetic polymorphisms in ABCB1 influence the pharmacodynamics of tacrolimus. *Ther Drug Monit*. 2013; 35(4):459–65. Epub 2013/06/08. [PubMed: 23743668]
58. Picard N. The pharmacokinetic interaction between mycophenolic acid and cyclosporine revisited: a commentary on “Mycophenolic acid glucuronide is transported by multidrug resistance-associated protein 2 and this transport is not inhibited by cyclosporine, tacrolimus or sirolimus”. *Xenobiotica; the fate of foreign compounds in biological systems*. 2013; 43(9):836–8. Epub 2013/01/24.
59. Woillard JB, Picard N, Thierry A, et al. Associations between polymorphisms in target, metabolism, or transport proteins of mycophenolate sodium and therapeutic or adverse effects in kidney transplant patients. *Pharmacogenet Genomics*. 2014; 24(5):256–62. Epub 2014/04/01. [PubMed: 24681964]

Key points

- Pharmacogenomics studies in CKD and dialysis patients are lacking, with investigation needed both for drugs specific to kidney therapy (like erythropoietin) as well as for drugs commonly used in these populations due to common comorbidities.
- To date, pharmacogenomics recommendations for ACEI and ARBs and blood pressure response based on RAS polymorphisms cannot be made.
- Adjusting the initial tacrolimus dose in kidney transplant recipients based on *CYP3A5* genotype may be useful, but studies on best dose and beneficial effect on long term outcome are still warranted. A higher dose is needed for *CYP3A5* expressers.
- Newly described variants important to tacrolimus pharmacokinetics (*CYP3A4**22, *POR**28, and *PPARA*) as well as multiple variants for pharmacodynamic outcomes like calcineurin inhibitor toxicity and NODAT await validation.
- For clinical implementation, pharmacogenetic variants must be validated in appropriate populations and show consistent evidence, preferably in the form of randomized control trials, that implementation affects outcomes.

Table 1

Summary of discussed pharmacogenetic variants related to pharmacokinetics of kidney transplant immunosuppression*

Drug	Genotype (rs number)	Phenotype	Reference
Tacrolimus	<i>CYP3A5</i> *3 (rs776746)	*3 homozygotes (<i>CYP3A5</i> non-expressers) have higher dose-adjusted trough blood concentrations and lower dose requirements compared to *1 carriers; evaluated in a randomized control trial with no effect on 3 month outcomes	(13–24, 36)
	<i>ABCB1</i> 3435C>T (rs1045642) 2677G>A/T (rs2032582) 1236C>T (rs1128503)	No clear effect on pharmacokinetics	(23, 27)
	<i>CYP3A4</i> *22 (rs35599367)	May explain additional variability in dose-adjusted blood concentration in combination with <i>CYP3A5</i> *1/*3	(22, 23, 29–31)
	<i>POR</i> *28 (rs1057868)	Associated with lower dose-adjusted blood concentration but only in <i>CYP3A5</i> expressers	(21, 32–34)
	<i>PPARA</i> (rs4253728 and rs4823613)	Associated with dose adjusted blood concentration but results conflicting	(21, 35)
Cyclosporine	<i>CYP3A5</i> *3 (rs776746)	No clear effect on pharmacokinetics	(13)
	<i>ABCB1</i> 3435C>T (rs1045642) 2677G>A/T (rs2032582) 1236C>T (rs1128503)	No clear effect on pharmacokinetics	(27)
	<i>CYP3A4</i> *22 (rs35599367)	Associated with higher dose-adjusted blood concentration	(21, 29, 30)
	<i>POR</i> *28 (rs1057868)	Associated with lower dose-adjusted blood concentration in <i>CYP3A5</i> non-expressers	(32)
Mycophenolate	<i>UGT1A9</i> (rs6714486) (rs17868320)	Associated with lower MPA exposure	(8, 37)
Sirolimus	<i>CYP3A5</i> *3 (rs776746)	Associated with higher dose-adjusted blood concentration	(38)
Everolimus	<i>CYP3A5</i> *3 (rs776746)	No clear effect on pharmacokinetics	(30, 39)

* List not exhaustive of all published literature but reflects recent publications or well established relationships

Abbreviations: MPA, mycophenolic acid

Table 2

Summary of discussed pharmacogenetic variants related to pharmacodynamics of kidney transplant immunosuppression*

Pharmacodynamic outcome	Genotype (rs number)	Result	Reference
Acute rejection	<i>CYP3A5</i> *3 (rs776746)	No clear effect with calcineurin inhibitors	(13, 24, 36, 44)
	<i>ABCB1</i> 3435C>T (rs1045642) 2677G>A/T (rs2032582) 1236C>T (rs1128503)	No clear effect with calcineurin inhibitors	(13, 24)
	<i>UGT1A9</i> (rs6714486) (rs17868320)	May be associated with acute rejection as a result of MPA underexposure	(8, 37)
	<i>IMPDH1</i>	May be associated with acute rejection in mycophenolate treated patients	(8, 45)
Calcineurin inhibitor nephrotoxicity	<i>ABCB1</i> 3435C>T (rs1045642) 2677G>A/T (rs2032582) 1236C>T (rs1128503)	No clear effect based on <i>recipient</i> genotype Related to nephrotoxicity based on <i>donor</i> genotype	(23, 27, 46)
New onset diabetes	<i>POR</i> *28 (rs1057868)	Associated with increased risk of NODAT	(47)
	<i>PPARA</i> (rs4253728 and rs4823613)	Associated with increased risk of NODAT	(47)
	Multiple SNPs in genes related to β -cell apoptosis	Associated with increased risk of NODAT	(48)
Sirolimus-related hyperlipidemia	<i>ABCB1</i> 3435C>T	Associated with higher total and low-density lipoprotein level-C cholesterol	(49)

* List not exhaustive of all published literature but reflects recent publications