Review

Mycophenolic acid pharmacogenomics in kidney transplantation

Fabiana Dalla Vecchia Genvigir[1], Alvaro Cerda[2], Thiago Dominguez Crespo Hirata[1], Mario Hiroyuki Hirata[1], Rosario Dominguez Crespo Hirata[1]

[1]Department of Clinical and Toxicological Analyses, School of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo 05508-000, Brazil.
[2]Department of Basic Sciences, Center of Excellence in Translational Medicine, CEMT-BIOREN, Universidad de La Frontera, Temuco 4810296, Chile.

Correspondence to: Prof. Rosario Dominguez Crespo Hirata, Department of Clinical and Toxicological Analyses, School of Pharmaceutical Sciences, University of Sao Paulo, Av. Prof. Lineu Prestes 580, Sao Paulo 05508-000, Brazil.
E-mail: rosariohirata@usp.br

Abstract

Mycophenolic acid (MPA) is a potent antiproliferative drug prescribed to prevent acute rejection in kidney transplantation. MPA reversibly inhibits the enzymes involved in the synthesis of guanosine nucleotides, thus preventing DNA replication of immune cells. Consequently, the repression of both cell and humoral immunity induces renal allograft tolerance. MPA is an effective and safe immunosuppressive drug, but some patients show variability in drug concentration, acute rejection, graft dysfunction, or MPA-related adverse events. Although the pharmacogenomics of immunosuppressive drugs has been widely investigated, MPA has been explored to a lesser extent. This review of MPA pharmacogenomic studies, included pharmacokinetics, adverse events, and main clinical outcomes of MPA treatment in kidney transplantation. Associations of variants in genes encoding MPA metabolizing enzymes, transporters, and targets with drug efficacy and safety are described. Most pharmacogenetic studies have focused on small sample sizes and few simultaneously analyzed genetic variants. Some studies reported significant associations of pharmacokinetics- and pharmacodynamics-related genes with MPA exposure, acute rejection, graft dysfunction, hematological events, and gastrointestinal complications. However, even large cohorts did not replicate the findings, possibly due to divergent study design, immunosuppressive scheme, follow-up time, and other factors. Finally, the heterogeneity of aspects between studies limit conclusions on pharmacogenetic biomarkers of MPA in kidney transplantation.

INTRODUCTION

Mycophenolic acid (MPA) is a potent antiproliferative drug broadly prescribed to prevent acute rejection in kidney transplantation. MPA is a reversible inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), an important enzyme involved in the *de novo* synthesis of guanosine nucleotides, which are essential for the proliferation of T and B cells[1,2]. Consequently, guanosine nucleotide depletion by MPA prevents DNA replication, leads to repression of both cell-and humoral-mediated immunity and induces tolerance to allograft in kidney transplantation[1,3,4].

IMPDH activity results from the expression of two isoforms, IMPDH type I and type II, which are encoded by *IMPDH1* and *IMPDH2*, respectively[2]. Both genes are constitutively expressed in most tissues, though activated T and B lymphocytes have a higher expression of *IMPDH2*[1]. Also, IMPDH type II has a higher affinity for MPA compared to IMPDH type I, which makes it a selective and potent antiproliferative drug for T and B cells[1,3] [Figure 1].

MPA is available either as an ester prodrug or as a sodium salt, which are equivalent in terms of therapeutic effect and MPA exposure[5]. The prodrug 2-morpholinoethyl ester, named mycophenolate mofetil (MMF), is converted to the active metabolite MPA by carboxylesterases 1 and 2 (CES1 and CES2)[6].

MPA is considered a safe drug even though some adverse events may occur, such as gastrointestinal complications, myelotoxicity, susceptibility to infections and neoplasms[1,3]. Designed to reduce gastrointestinal adverse events, the enteric-coated mycophenolate sodium salt (EC-MPS) has a delayed release formulation that delivers mycophenolate in the small intestine[7]. Due to enteric coating, EC-MPS causes a slower absorption than MMF, and more variable time for MPA to reach maximal concentration[8].

MPA is extensively converted (about 90%) to the inactive 7-O-glucuronide (MPAG), by UDP-glucuronosyltransferases (UGTs), mainly in the liver but also in intestine and to a minor extent in the kidney[9]. This process is mediated in the liver and kidney by UGT1A9, whereas UGT1A8 plays a key role in the intestine with minor contribution from the other UGTs[9] [Figure 1]. Since MPA and MPAG are bound to serum albumin, an accumulation of MPAG may compete with free MPA for albumin and lead to increased free MPA concentration in plasma[9,10].

UGT2B7, with minor contribution of UGT1A8, mediates the biotransformation of MPA to its acyl-glucuronide form (AcMPAG) [Figure 1]. This metabolite can inhibit the activity of IMPDH and is therefore pharmacologically active[11]. The cytochrome P450 (CYP) family also plays a role in MPA biotransformation. The 6-O-desmethyl-MPA (DM-MPA) is a phase I metabolite of MPA produced in the liver by the activity of CYP3A4, CYP3A5, and to a lesser extent by CYP2C8[12].

MPAG and AcMPAG, but not MPA, are excreted in the bile. The incorporation of these metabolites into hepatocytes is mediated by organic anion transport polypeptides (OATPs)[13,14], which are membrane influx transporters encoded by genes of the *SLCO* family. From the hepatocyte, MPAG and AcMPAG are excreted in the bile via ATP-binding cassette subfamily C member 2 (ABCC2), also named multidrug resistance-associated protein 2 (MRP2)[15,16]. ABC transporters are ATP-dependent drug efflux pumps[17]. Another important member is ABCB1 (also known as P-glycoprotein or multidrug resistance protein 1-MDR1), which seems to play a role in MPA disposition[18].
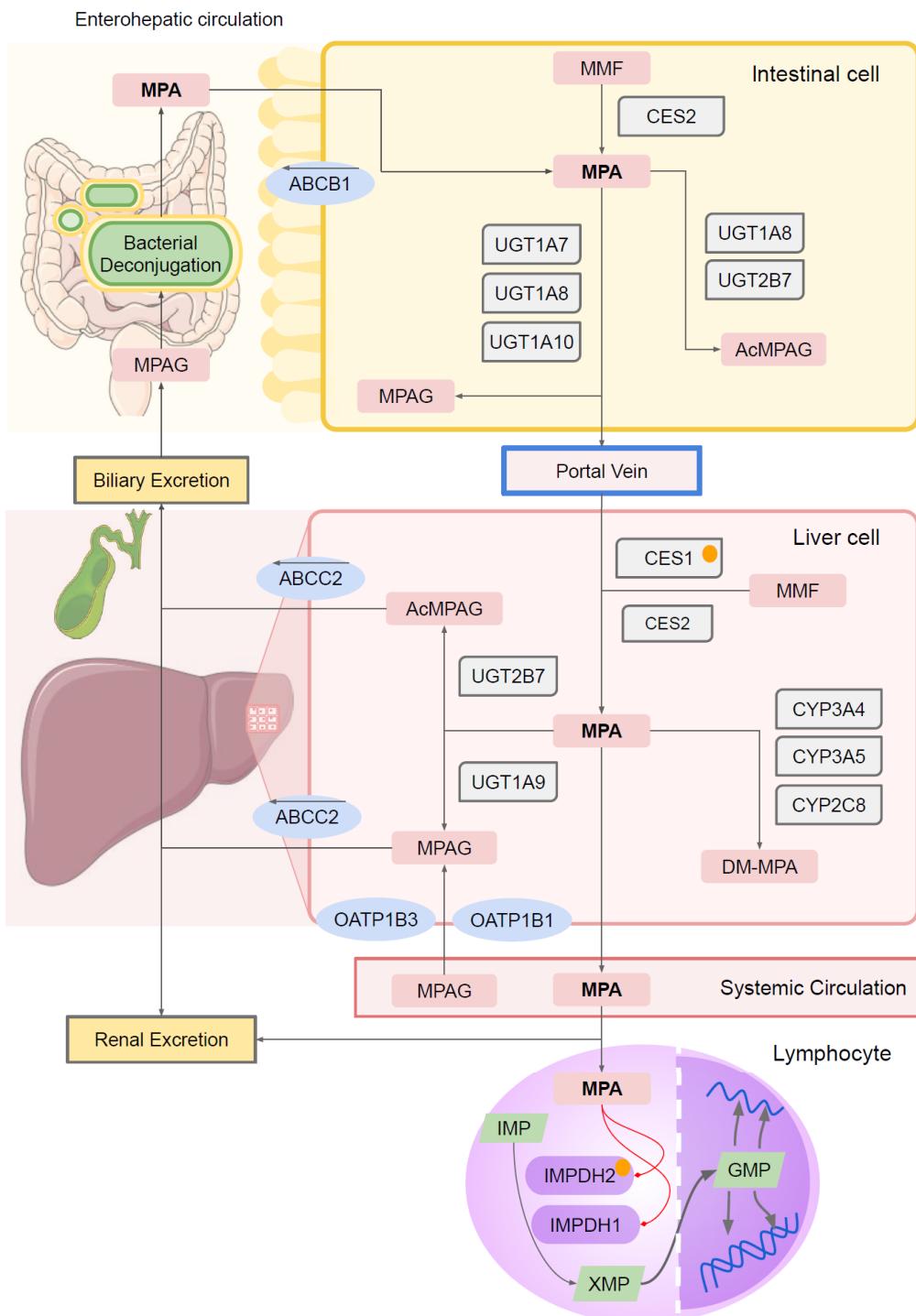
Figure 1. Schematic representation of MPA pharmacokinetics pathways and mechanisms of action. AcMPAG: acyl-MPA glucuronide; DM-MPA: 6-O-desmethyl MPA; GMP: guanosine 5'-monophosphate; IMP: inosine 5'-monophosphate; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MPAG: MPA-7-O-glucuronide; XMP: xanthosine 5'-monophosphate

MPAG excreted in the bile undergoes extensive enterohepatic recirculation, being hydrolyzed to MPA in the small intestine and reabsorbed [Figure 1]. The enterohepatic recirculation contributes 10%-60% of the total MPA exposure and causes a secondary peak 6-12 h after oral MPA administration[1]. MPA is also eliminated in the urine as MPA in negligible amounts, and mostly as MPAG, possibly mediated by ABCC2[19].

The more common MPA-related adverse events are diarrhea and other gastrointestinal complications. MMF can also cause myelotoxicity, especially leukopenia and anemia. Susceptibility to viral infections, such as cytomegalovirus (CMV) and BK polyomavirus (BKV), also increases in patients taking an MMF-containing triple therapy regimen. Patients with low tolerance to MPA may require dose reduction, temporary interruption, or permanent discontinuation of the MMF treatment[1].

The contribution of pharmacogenomics in the response to immunosuppressive drugs has been widely investigated. Several clinical studies have reported the influence of gene polymorphisms on the efficacy and safety of MPA, suggesting their potential contribution to transplant patient management[1-3].

This review explores the pharmacogenomic studies that investigated polymorphisms in genes involved in the pharmacokinetics and pharmacodynamics of MPA in kidney transplantation and the main clinical outcomes and adverse events.

GENES RELATED TO MPA PHARMACOKINETICS

The pharmacogenomic studies involving genes related to MPA-metabolizing enzymes and transporters are summarized in Tables 1 and 2, respectively.

CES1 and CES2

CES1 and CES2 play crucial roles in the hydrolysis of the MMF prodrug to MPA. CES1 is highly expressed in the liver, while showing extremely low levels in the intestine. On the other hand, CES2 is mainly expressed in the intestine, and also observed in liver tissue[20].

Fujiyama *et al.*[21] evaluated the influence of *CES2* variants in 5′UTR (-1548A>G, rs3890213) and intronic regions (4595A>G, rs2303218 and 8721C>T, rs2241409) on MPA pharmacokinetics. They found no association of these variants with MPA plasma concentration-time area under the curve, partial (AUC_{0-6}) and total (AUC_{0-12}, maximum plasma concentration (Cmax) and time required to reach the peak (Tmax) in 80 Japanese kidney recipients at 28 days after transplantation. These variants were also not associated with allograft rejection (AR) or diarrhea[21].

In a retrospective study with Brazilian patients a long time after transplantation (7.00 ± 5.71 years), *CES2* 8721TT genotype was associated with increased risk of AR (OR: 7.2; 95%CI: 1.1-46, $P = 0.038$), whereas the *CES1* 356C>T (rs62028647) variant was not associated with AR[22].

CYP3A4, CYP3A5 and CYP2C8

The CYP enzymes CYP3A4, CYP3A5 and possibly CYP2C8 can catalyze the generation of the phase 1 metabolite DM-MPA, evident in human liver samples[12], suggesting that variants in these genes may be involved in the clinical outcomes of MPA treatment.

Studies with certain variants in *CYP2C8* (rs11572080 and rs10509681), *CYP3A4* (rs2740574 and rs35599367) and *CYP3A5* (rs776746) found no association with MPA trough concentration/dose ratio (C/D) and AUC_{0-12} in kidney transplantation[23,24].

Although the *CYP3A4* and *CYP3A5* variants did not influence the clinical outcomes of MPA-based therapy[23-27], the results were less consistent regarding *CYP2C8* variants.

CYP2C8 rs11572076 (G>A) variant was associated with increased risk of anemia (OR: 3.2, 95%CI: 1.7-6.2, $P < 0.001$) in a study that evaluated 2,724 variants in 978 adult kidney or simultaneous kidney-pancreas recipients[28]. The authors also found no association between this variant and leukopenia, a finding later

Table 1. Genes related to mycophenolic acid metabolism in kidney transplantation

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
CES1	rs62028647 (356C>T)	356T: 46%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	No association of CES1 356C>T variant with AR	[22]
CES2	rs3890213 (-1548A>G) rs2303218 (4595A>G)	-	Prospective	80 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of CES2 -1548A>G, 4595A>G and 8721C>T variants with MPA pharmacokinetics	No association of CES2 -1548A>G, 4595A>G and 8721C>T variants with AR or diarrhea	[21]
	rs2241409 (8721C>T)	8721T: 22%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	CES2 8721TT genotype was associated with increased risk of AR	[22]
CYP2C8	rs11572076 G>A	-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of CYP2C8 rs11572076 variant with leukopenia	[27]
		rs11572076A: 0.5%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	CYP2C8 rs11572076GG genotype was associated with reduced risk of leukopenia. No association with AR, diarrhea, or anemia	[29]
	CYP2C8*3 [rs11572080 (c.416G>A) + rs10509681 (c.1196A>G)]	CYP2C8*3: 9%	Prospective, multicenter	148 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids Three-month follow-up	-	CYP2C8*3 variant was associated with higher eGFR in CYP3A5-non-expressing patients. No association of CYP2C8*3 variant with AR, DGF or adverse events	[30]
		c.416A: 9% c.1196G:10%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroid One-year follow-up	No association of CYP2C8*3 variant with MPA C/D	CYP2C8*3 variant was associated with higher eGFR at week 2 and month 1. No association of CYP2C8*3 variant with AR	[24]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
CYP3AA4	rs2740574 (CYP3A4*1B, -392A>G)	-392G: 5%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	-	No association of CYP3A4 -392A>G variant with AR	[25]
		CYP3A4*1B(G): 21%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of CYP3A4*1B variant with MPA C/D	No association of CYP3A4*1B variant with DGF or AR	[24]
	rs35599367 (CYP3A4*22)	-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of CYP3A4*22 variant with leukopenia	[27]
		CYP3A4*22 (T): 2%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of CYP3A4*22 variant with MPA C/D	No association of CYP3A4*22 variant with DGF or AR	[24]
CYP3A5	rs776746 (CYP3A5*3, g.6986A>G)	CYP3A5*3(G):78%	Prospective	30 adult patients (Japan)	MMF Tacrolimus Corticosteroids Six-week follow-up	No association of CYP3A5*3 variant with daytime and nighttime MPA AUC_{0-12}	No association of CYP3A5*3 variant with AR or gastrointestinal adverse events	[23]
		CYP3A5*1(A): 9%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	-	No association of CYP3A5*3 variant with AR	[25]
		CYP3A5*3(G): 95%	Retrospective	207 pediatric patients (Poland)	MMF or Azathioprine Cyclosporine Tacrolimus Corticosteroids	-	No association of CYP3A5*3 variant with MMF-related toxicity	[26]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of CYP3A5*3 variant with leukopenia	[27]
		CYP3A5*1(A): 29%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of CYP3A5*3 variant with MPA C/D	No association of CYP3A5*3 variant with DGF or AR	[24]
UGT1A1	rs3064744 (UGT1A1*28, A(TA)6TAA > A(TA)7TAA)	UGT1A1*28: 7%	Prospective	30 adult patients (Japan)	MMF Tacrolimus Corticosteroids Six-week follow-up	No association of UGT1A1*28 variant with daytime and nighttime MPA AUC_{0-12}	No association of UGT1A1*28 variant with AR or gastrointestinal adverse events	[23]

Table 1. Genes related to mycophenolic acid metabolism in kidney transplantation

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
	(-57T>G)		...(Case-Control), multicenter	...4 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of UGT1A7 -57T>G variant with leukopenia	[27]
	rs11692021 (c.622T>C)	UGT1A7*2: 8% UGT1A7*3: 28%	Prospective	80 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of UGT1A7*2 and UGT1A7*3 variants with MPA pharmacokinetics	-	[33]
	UGT1A7*2 [c.387T>G (rs17868323) + c.391C>A (rs17863778) + c.392G>A (rs17868324)]	c.622C: 37%	Retrospective	256 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Up to 115-month follow-up	-	No association of UGT1A7 c.622C>T variant with gastrointestinal adverse events	[34]
	UGT1A7*3 (c.387T>G + c.391C>A + c.392G>A + c.622T>C)	c.622C: 19%	Prospective	127 adult patients (China)	MMF Tacrolimus Corticosteroids	UGT1A7 c.622CC genotype was associated with higher exposure to MPAG (AUC$_{0-12}$)	-	[35]
UGT1A8	rs17863762 (UGT1A8*3, c.830G>A) rs1042597 (UGT1A8*2, c.518C>G)	-	Retrospective	74 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	Treatment with MMF 2 g/d and UGT1A8 c.830AA genotype were associated with occurrence of infections, but not diarrhea, or blood disorders	[42]
		UGT1A8*2: 58%	Prospective	72 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of UGT1A8*2 variant with daytime or nighttime MPA pharmacokinetics	-	[36]
		c.830A: 4%	Retrospective (Case-Control)	38 pediatric patients (USA)	MMF Cyclosporine Tacrolimus Corticosteroids	-	No association of UGT1A8 c.830G>A variant with adverse events (diarrhea or leukopenia)	[43]
		c.518G: 25% c.830A: 2%	Prospective, multicenter (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	UGT1A8*2/*2 (GG) genotype was associated with higher MPA AUC$_{0-12}$ in cyclosporine-treated patients	No association of UGT1A8 c.518C>G and c.830G>A variants with AR	[39]
		c.518G: 26%	Prospective (included multicenter Apomygre study)	185 patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids At a point between 3-6 months	No association of UGT1A8 c.518C>G variant with MPA or MPAG pharmacokinetics	-	[14]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.518G: 23% c.830A: 2%	Retrospective	256 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Up to 115-month follow-up	-	*UGT1A8* c.518G allele was associated with low risk of diarrhea, on cyclosporine treatment	[34]
		c.830A: 1%	Prospective, multicenter	89 pediatric patients (France)	MMF Cyclosporine Tacrolimus Corticosteroids Sixty-day follow-up	No association of *UGT1A8* c.830G>A variant with MPA pharmacokinetics	-	[40]
		c.518G: 43%	Prospective, Multicenter (Case-control)	37 adult patients (China)	MMF Cyclosporine Corticosteroids	No association of *UGT1A8* c.518C>G variant with MPA or MPAG exposure (AUC_{4-12} or AUC_{0-12})	-	[37]
		c.518G: 32%	Prospective	109 adult patients (USA)	MMF EC-MPS Cyclosporine Tacrolimus Corticosteroids Six-month follow-up	-	*UGT1A8* c.518GG genotype was associated with higher gastrointestinal symptom rating scale (GSRS) score up two weeks	[41]
		c.518G: 25%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	No association of *UGT1A8* c.518C>G variant with AR or adverse events	[29]
		c.518G: 52%	Prospective	127 adult patients (China)	MMF Tacrolimus Corticosteroids	*UGT1A8* c.518G allele was associated with lower MPAG AUC_{0-12}	-	[35]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *UGT1A8*2* and *UGT1A8*3* variants with leukopenia	[27]
		c.518G: 49%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	No association of *UGT1A8* c.518C>G variant with MPA C/D (days 3-8)	-	[38]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
UGT1A9	rs17868320 (c.-2152C>T) rs6731242 (-1887T>G) rs13418420 (-1818T>C)	c.-2152T: 7% c.-275A: 9% c.98C: 2%	Prospective	95 adult patients (Belgium)	MMF Tacrolimus Corticosteroids One-year follow-up	Treatment with MMF 2g (n = 32) and UGT1A9 c.-2152T and/or c.-275A alleles were associated with MPA pharmacokinetics, including lower $AUC_{0-12 \text{ and } 6-12}$, at 7 days post-transplantation	No association of UGT1A9 c.-2152C>T, c.-275T>A or c.98T>C variants with AR or adverse events	[47]
	rs10176426 (-665C>T) rs2741045 (c.-440C>T) rs2741046 (c.-331T>C)	c.-2152T: 1% -1887G: 13% -665T: 4% -440/-331 T/C: 41% c.-275A: 5% c.98C: 0%	Mixed	40 adult patients (Italy)	MMF Cyclosporine Corticosteroid-free At Month 6	UGT1A9 -665CT genotype was associated with higher MPA C/D and c.-440/c.-331TT/CC genotypes were associated with higher MPA exposure ($AUC_{0-2, 0-4 \text{ and } 0-12}$)	No association of UGT1A9 c.-440C>T (or c.-331T>C) variant with gastrointestinal adverse events	[48]
	rs6714486 (c.-275T>A)	I399C: 36%	Prospective	80 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of UGT1A9 I399T>C variant with MPA pharmacokinetics	-	[33]
	rs3832043 (-118delT) rs72551330 (UGT1A9*3, c.98T>C) rs2741049 (I399 T>C)	-	Prospective	100 adult patients (Belgium)	MMF Tacrolimus Corticosteroids Five-year follow-up	UGT1A9 c.-275T>A and/or c.-2152C>T variant was associated with low MPA exposure (AUC_{0-12} < 30 mg/L. h^{-1}).	-	[45]
		c.-2152T: 9% -331C: 28% c.-275A: 11% c.98C: 0%	Retrospective (Case-Control)	38 pediatric patients (USA)	MMF Cyclosporine Tacrolimus Corticosteroids	-	UGT1A9 c.-331C allele was associated with adverse events (especially leukopenia)	[43]
		c.-2152T: 5% c.-275A: 6% c.98C: 2% I399T: 38%	Prospective, multicenter (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	UGT1A9 c.-2152CT and c.-275TA genotypes were associated with lower MPA AUC_{0-12}, on tacrolimus treatment, especially at day 3. c.98TC genotype was associated with higher AUC_{0-12}	UGT1A9 c.-2152CT and/or c.-275TA genotypes was associated with increased risk for AR, on tacrolimus treatment	[39]
		-	Mixed (Case-control)	133 adult patients - for PK profile n = 30 (Spain)	MMF EC-MPS Tacrolimus	UGT1A9 c.-275A (or c.-2152T) allele was associated with lower MPA exposure (AUC_{0-12} or AUC_{6-12})	UGT1A9 c.-275A (or c.-2152T) allele was associated with more admissions due to gastrointestinal adverse events	[46]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.-2152T: 6% c.-440T: 24% c.-275A:6% c.98C: 3%	Prospective (included multicenter Apomygre study)	185 patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids At a point between 3-6 months	No association of *UGT1A9* c.-2152C>T, c.-440C>T, c.-275T>A and c.98T>C variants with MPA or MPAG pharmacokinetics	-	[14]
		c.-275A: 6%	Retrospective	256 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Up to 115 month follow-up	-	No association of *UGT1A9* c.-275T>A variant with gastrointestinal adverse events	[34]
		c.-2152T: 4% c.-275A: 6% c.98C: 2%	Prospective, multicenter	89 pediatric patients (France)	MMF Cyclosporine Tacrolimus Corticosteroids Sixty-day follow-up	No association of *UGT1A9* c.-2152C>T, c.-275T>A and c.98T>C variants with MPA pharmacokinetics	-	[40]
		c.-275A: 7% c.98C: 1%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	No association of *UGT1A9* c.-275T>A and c.98T>C variants with AR or adverse events	[13]
		c.-2152T: 5% c.-275A: 4% c.98C: 3%	Retrospective (Case-control)	103 adult patients (Poland)	MMF Calcineurin inhibitors Corticosteroids One-year follow-up	-	*UGT1A9* c.98TC genotype was associated with decreased graft function	[51]
		c.98C: 4%	Retrospective	140 adult patients (Poland)	MMF Cyclosporine Corticosteroids	-	*UGT1A9* c.98TC genotype was associated with lower eGFR, but not with AR and DGF	[52]
		c.-2152T: 3% c.-275A: 5%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	No association of *UGT1A9* c.-2152C>T and c.-275T>A variants with AR or adverse events	[29]
		-1818T: 13% c.-440T: 2% c.-331C: 2% -118delT: 58% I399C: 31%	Prospective	127 adult patients (China)	MMF Tacrolimus Corticosteroids	*UGT1A9* c.-440CT (or c.-331TC) and -1818CC genotypes were associated with higher and lower MPAG AUC$_{0-12}$, respectively	-	[35]
		-	Retrospective (Case-control) multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *UGT1A9* c.-2152C>T, -665C>T, c.-440C>T and c.-275T>A variants with leukopenia	[27]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		-	Retrospective	118 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids	No association of UGT1A9 -118delT variant with MPA pharmacokinetics	--	[50]
		-	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	No association of UGT1A9 c.-275T>A variant with AR	[22]
		c.-275A: 14% c.98C: 0%	Prospective	21 adult patients (Canada)	MMF Tacrolimus Corticosteroid-free One-year follow-up	No association of UGT1A9 c.-275T>A and c.98T>C variants with MPA exposure (AUC)	No association of UGT1A9 c.-275T>A and c.98T>C variants with neutrophil counts	[49]
		c.-440T: 3% c.-331C: 3% c.I399C: 47%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	No association of UGT1A9 c.-440C>T, c.-331T>C and I399 T>C variants with MPA C/D (days 3-8)	-	[38]
	rs6744284	rs6744284T: 32%	Prospective	109 adult patients (USA)	MMF EC-MPS Cyclosporine Tacrolimus Corticosteroids Six-month follow-up	-	UGT1A9 rs6744284CC genotype was associated with higher gastrointestinal symptom rating scale (GSRS) score for constipation at week 1	[41]
UGT2B7	rs7438135 (c.-840G>A, c.-842G>A or c.-900G>A)	c.-842G: 55% 802T: 55%	Prospective, multicenter	92 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids Three-month follow-up	UGT2B7 c.-842AA (802CC) genotype was associated with higher AcMPAG AUC_{0-9} at Month 1 and 3, on sirolimus treatment (n = 40)	-	[53]
	rs7662029 (c.-327G>A) rs73823859 (-79G>A)	802T: 41%	Mixed	40 adult patients (Italy)	MMF Cyclosporine Corticosteroid-free At Month 6	UGT2B7 802TT genotype individuals showed higher MPA peak concentration than those with 802CC genotype	-	[48]
	rs12233719 (c.211G>T) rs7439366 (802C>T, UGT2B7*2)	UGT2B7*2(T): 33%	Prospective	72 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of UGT2B7*2 variant with daytime or nighttime MPA pharmacokinetics	-	[36]
	rs62298861 (IVS1+985A>G)	c.-840G: 50%	Prospective (FDCC Study)	332 adult patients	MMF Cyclosporine Tacrolimus Corticosteroid One-year follow-up	No association of UGT2B7 c.-840G>A variant with exposure to AcMPAG (level and AUCs)	No association of UGT2B7 c.-840G>A variant with diarrhea or leukopenia	[54]
		c.-900G:45%	Retrospective (Case-control)	38 pediatric patients (USA)	MMF Cyclosporine Tacrolimus Corticosteroids	-	No association of UGT2B7 c.-900A>G variant with adverse events (diarrhea and leukopenia)	[43]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.-842A: 50% -79A: 2% 802C: 50%	Prospective, multicenter (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *UGT2B7* c.-842G>A, -79G>A and 802C>T variants with MPA exposure (AUC_{0-12})	No association of *UGT2B7* c.-842G>A, -79G>A and 802C>T variants with AR	[39]
		c.-840A: 48%	Retrospective	256 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Up to 115-month follow-up	-	No association of *UGT2B7* c.-840G>A variant with gastrointestinal adverse events	[34]
		802T: 48%	Prospective, multicenter	89 pediatric patients (France)	MMF Cyclosporine Tacrolimus Corticosteroids Sixty-day follow-up	*UGT2B7* 802T allele was associated with higher MPA apparent oral clearance	-	[40]
		802T: 46%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	No association of *UGT2B7* 802C>T variant with AR or adverse events	[13]
		c.-840G: 47%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	*UGT2B7* c.-840G allele was associated with increased risk of anemia. No association with AR, diarrhea, or leukopenia	[29]
		c.-900G: 29% IVS1+985G: 5% c.211T: 14%	Prospective	127 adult patients (China)	MMF Tacrolimus Corticosteroids	*UGT2B7* IVS1+985AG genotype was associated with higher MPA AUC_{0-12}	-	[35]
		-	Retrospective (Case-control) multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	In patients treated non-depleting antibodies, *UGT2B7* c.-900G allele was associated with increased risk of leukopenia	[27]
		c.211T: 34%	Retrospective	118 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids	*UGT2B7* c.211G>T variant was associated with MPA initial volume of distribution and c.211GT genotype was associated with higher MPA exposure	-	[50]
		c.-842G: 37%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	*UGT2B7* c.-842G allele was associated with prevention of AR	[22]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.211T: 5% 802T: 10%	Prospective	21 adult patients (Canada)	MMF Tacrolimus Corticosteroid-free One-year follow-up	No association of *UGT2B7* c.211G>T and 802C>T variants with MPA exposure (AUC)	No association of *UGT2B7* c.211G>T and 802C>T variants with neutrophil count	[49]
		c.211T: 12% c.-327A: 30%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	*UGT2B7* rs7662029 GG genotype was possibly associated with higher MPA C/D (days 3-8)	-	[38]
	rs28365063 (c.372A>G)	c.372G: 14%	Prospective, multicenter	148 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids Three-month follow-up	-	No association of *UGT2B7* c.372A>G variant with AR, DGF, graft function or adverse events	[30]

AcMPAG: acyl-MPA-glucuronide; AR: allograft rejection; AUC: area under the concentration-time curve; C/D: trough dose-adjusted concentration; DGF: delayed graft function; EC-MPS: enteric-coated mycophenolate sodium salt; eGFR: estimated glomerular filtration rate; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MPAG: MPA-7-O-glucuronide

Table 2. Genes related to mycophenolic acid transport in kidney transplantation

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
ABCB1	rs9282564 (61A>G) rs3842 (417A>G) rs1128503 (c. 1236C>T) rs2032582 (c.2677G>T/A) rs1045642 (c.3435C>T)	c.3435T: 42%	Prospective	30 adult patients (Japan)	MMF Tacrolimus Corticosteroids Six-week follow-up	No association of *ABCB1* c.3435C>T variant with daytime and nighttime MPA AUC_{0-12}	*ABCB1* c.3435T allele was associated with higher requirement of MMF dose reduction due to diarrhea. No association of *ABCB1* c.3435C>T variant with AR	[23]
		c. 1236T: 40% c. 2677G: 58% c.3435T: 49% 417G: 13% 61G: 9%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	-	*ABCB1* c.2677T allele and c.3435T/c.2677T/c.1236T haplotype was associated with increased risk of AR	[25]
		c.3435T: 55%	Retrospective	207 pediatric patients (Poland)	MMF or Azathioprine Cyclosporine Tacrolimus Corticosteroids	-	No association of *ABCB1* c.3435C>T variant with MMF-related toxicity	[26]
		c.3435T: 41%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	No association of *ABCB1* c.3435C>T variant with AR or adverse events	[13]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.1236T: 41% c.3435T: 50%	Prospective (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *ABCB1* c.1236C>T, c.2677G>T/A and c.3435C>T variants with exposure to MPA, MPAG or AcMPAG	No association of *ABCB1* c.1236C>T, c.2677G>T/A and c.3435C>T variants with diarrhea or leukopenia	[59]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *ABCB1* c.1236C>T, c.2677G>T/A and c.3435C>T variants with leukopenia	[27]
		c.1236T: 36% c. 2677T/A: 32/4%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of *ABCB1* c.1236C>T and c 2677G>T/A variants with MPA C/D	No association of *ABCB1* c.1236C>T and c.2677G>T/A variants with DGF or AR	[24]
ABCC2	rs1885301 (-1549G>A) rs7910642 (-1023G>A) rs2804402 (-1019A>G) rs717620 (c.-24C>T)	-1549A: 38% -1023A: 13% -1019G: 43% c.-24T: 23% c.1249A: 17% c.3972T: 32% c.4544A: 9%	Prospective	95 adult patients (Belgium)	MMF Tacrolimus Corticosteroids One-year follow-up	*ABCC2* c.-24C>T and c.3972C>T variants were associated with protection from a reduction in MPA exposure (AUC$_{0-12}$) in patients with liver dysfunction, at day 7. In stable kidney recipients, c.-24T allele was associated with higher MPA C/D	*ABCC2* c.-24T allele was associated with diarrhea. No association of *ABCC2* c.-24C>T variant with AR or hematological disorders	[62]
	rs2273697 (c.1249G>A) rs113646094 (1446C>G)	c.-24T: 20% c.1249A: 28%	Mixed	40 adult patients (Italy)	MMF Cyclosporine Corticosteroid-free At Month 6	No association of *ABCC2* c.-24C>T or 1249G>A variants with MPA or MPAG exposure	-	[48]
	rs8187694 (3563T>A) rs17222723 (3600T>A)	c.-24T: 26%	Prospective	87 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of *ABCC2* c.-24C>T variant with MPA pharmacokinetics	No association of *ABCC2* c.-24C>T variant with diarrhea	[65]
	rs3740066 (c.3972C>T) rs8187710 (c.4544G>A)	c.3972T: 36% rs2804402G: 42% rs17222723A: 7%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	-	No association of *ABCC2* c.3972C>T, rs2804402 and rs17222723 variants with AR	[25]
	rs12762549	-	Prospective	100 adult patients (Belgium)	MMF Tacrolimus Corticosteroids Five-year follow-up	No association of *ABCC2* c.-24C>T variant with MPA exposure	-	[45]
	rs2804402	c.-24T: 18% c.3972T: 34%	Prospective, multicenter (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *ABCC2* c.-24C>T and c.3972C>T variants with MPA exposure (AUC$_{0-12}$)	No association of *ABCC2* c.-24C>T and c.3972C>T variants with AR	[39]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.-24T: 23%	Prospective (included multicenter Apomygre study)	185 patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids At a point between 3-6 months	No association of ABCC2 c.-24C>T variant with MPA or MPAG pharmacokinetics	-	[14]
		c.-24T: 24% c.3972T: 39%	Retrospective	256 adult patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Up to 115-month follow-up	-	No association of ABCC2 c.-24C>T and c.3972C>T variants with gastrointestinal adverse events	[34]
		c.-24T:19% c.1249A: 19% 3563A: 10% c.3972T:35%	Prospective, multicenter	89 pediatric patients (France)	MMF Cyclosporine Tacrolimus Corticosteroids Sixty-day follow-up	No association of ABCC2 c.-24C>T, c.1249G>A, 3563T>A and c.3972C>T variants with MPA pharmacokinetics	-	[40]
		c.-24T: 19% c.1249A: 19% 1446G: 0.7% c.3972T: 35%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	No association of ABCC2 c.-24C>T, c.1249G>A, 1446C>G and c.3972C>T variants with AR or adverse events	[13]
		c.-24T: 21% c.3972T: 23%	Prospective, multicenter (Symphony study)	55 adult patients (Spain)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids Three-month follow-up	ABCC2 c.-24T allele was associated with lower MPA AUC, on cyclosporine-free treatment	-	[63]
		c.-24T: 28%	Prospective, Multicenter (Case-control)	37 adult patients (China)	MMF Cyclosporine Prednisone	No association of ABCC2 c.-24T variant with MPA or MPAG exposure (AUC_{4-12} or AUC_{0-12})	-	[37]
		c.-24T: 19% c.3972T: 36%	Prospective, multicenter (Symphony study)	56 adult patients	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	No association of ABCC2 c.-24C>T and c.3972C>T variants with MPA (or its metabolites) exposure	-	[66]
		c.-24T: 17% c.1249A: 21% c.3972T: 39% c.4544A: 8%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	No association of ABCC2 c.-24C>T, c.1249G>A, c.3972C>T and c.4544G>A variants with AR or adverse events	[29]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.-24T: 14% c.3972T: 32%	Prospective, multicenter	148 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids Three-month follow-up	-	No association of *ABCC2* c.-24C>T and c.3972C>T variants with AR, DGF, graft function or adverse events	[30]
		c.-24T: 17% c.1249A: 24%	Prospective	68 adult patients (Croatia)	MMF EC-MPS Cyclosporine Tacrolimus Corticosteroids	Donors' *ABCC2* c.1249A allele was associated with a reduced peak and early (AUC$_{0-2}$) exposure to MPA	-	[64]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *ABCC2* c.-24C>T and rs12762549 variants with leukopenia	[27]
		c.-24T: 20% c.1249A: 22%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	No association of *ABCC2* c.-24C>T and c.1249G>A variants with AR	[22]
		c.1249A: 19% c.3972T: 30%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of *ABCC2* c.1249G>A and c.3972C>T variants with MPA C/D	No association of *ABCC2* c.1249G>A and c.3972C>T variants with DGF or AR	[24]
		c.-24T: 19% c.1249A: 0%	Prospective	21 adult patients (Canada)	MMF Tacrolimus Corticosteroid-free One-year follow-up	No association of *ABCC2* c.-24C>T and c.1249G>A variants with MPA exposure (AUC)	No association of *ABCC2* c.-24C>T and c.1249G>A variants with neutrophil counts	[49]
		c.-24T: 21% c.1249A: 8%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	*ABCC2* c.-24TT genotype was possibly associated with higher MPA C/D (days 3-8)	-	[38]
ABCG2	rs2231142 (c.421C>A) rs4491984G>A	c.421A: 26%	Prospective, Multicenter (Case-control)	37 adult patients (China)	MMF Cyclosporine Corticosteroids	No association of *ABCG2* c.421C>A variant with MPA or MPAG exposure (AUC$_{4-12}$ or AUC$_{0-12}$)	-	[37]
		c.421A: 8%	Prospective, multicenter	148 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids Three-month follow-up	-	No association of *ABCG2* c.421C>A variant with AR, DGF, graft function or adverse events	[30]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *ABCG2* c.421C>A variant with leukopenia	[27]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.421A: 10%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of *ABCG2* c.421C>A variant with MPA C/D	No association of *ABCG2* c.421C>A variant with DGF or AR	[24]
		c.421A: 31% rs4491984A: 50%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	No association of *ABCG2* c.421C>A and rs4491984 variants with MPA C/D (days 3-8)	-	[38]
SLCO1B1	rs4149015 (-11187G>A) rs2306283 (c.388A>G)	*SLCO1B1*1A*: 32% *SLCO1B1*1B*: 50% *SLCO1B1*15*: 18%	Prospective	87 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of *SLCO1B1* *1A, *1B and *15 variants with MPA pharmacokinetics	No association of *SLCO1B1* *1A, *1B and *15 variants with diarrhea	[65]
	rs11045819 (463C>A) rs4149056 (c.521T>C or Val174Ala)	-11187A: 6% c.388A: 50% c.521C: 14%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	*SLCO1B1* c.521C allele was associated with reduced MPA-related adverse events, on cyclosporine-free treatment	[13]
	rs11045819 (Pro155Thr)	c.388G: 44% 463A: 14% c.521C: 18%	Prospective (included multicenter Apomygre study)	185 patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids At a point between 3-6 months	No association of *SLCO1B1* c.388A>G, 463C>A and c.521T>C variants with MPA or MPAG pharmacokinetics	-	[14]
		c.388G: 46% c.521C: 17%	Prospective (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *SLCO1B1* c.388A>G and c.521T>C variants with exposure to MPA, MPAG or AcMPAG	No association of *SLCO1B1* c.388A>G and c.521T>C variants with diarrhea or leukopenia	[59]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *SLCO1B1* rs4149056 and rs11045819 variants with leukopenia	[27]
		c.521C: 20%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids	-	No association of *SLCO1B1* c.521T>C variant with AR	[22]
		c.388A: 44% c.521C: 14%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of *SLCO1B1* c.388A>G and c.521T>C variants with MPA C/D	No association of *SLCO1B1* c.388A>G and c.521T>C variants with DGF or AR	[24]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
		c.388G: 48% 463A: 10%	Prospective	21 adult patients (Canada)	MMF Tacrolimus Corticosteroid-free One-year follow-up	No association of *SLCO1B1* c.388A>G and 463C>A variants with MPA exposure (AUC)	No association of *SLCO1B1* c.388A>G and 463C>A variants with neutrophil counts	[49]
SLCO1B3	rs4149117 (c.334T>G) rs7311358 (c.699G>A) rs1104585 rs60140950 (c.767G>C)	c.334T: 34% 699G: 34%	Prospective	87 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	*SLCO1B3* c.334GG (699AA) genotype was associated with higher exposure to MPA (AUC$_{6\text{-}12}$)	No association of *SLCO1B3* c.334T>G (or 699G>A) variant with diarrhea	[65]
		c.334T: 17%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	-	No association of *SLCO1B3* c.334T>G variant with AR or adverse events	[13]
		c.334T: 18% 767C: 15%	Prospective (included multicenter Apomygre study)	185 patients (France)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids At a point between 3-6 months	*SLCO1B3* c.334GG genotype was associated with lower MPA peak concentration and exposure (AUC$_{0\text{-}12}$) and higher MPAG/MPA ratio, on cyclosporine-free treatment ($n = 70$)	-	[14]
		c.334T: 19%	Prospective (FDCC Study)	338 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *SLCO1B3* c.334T>G (or 699G>A) variant with exposure to MPA, MPAG or AcMPAG	No association of *SLCO1B3* c.334T>G (or 699G>A) variant with diarrhea or leukopenia	[59]
		c.334T: 30%	Prospective, Multicenter (Case-control)	37 adult patients (China)	MMF Cyclosporine Corticosteroids	No association of *SLCO1B3* c.334T>G variant with MPA or MPAG exposure (AUC$_{4\text{-}12}$ or AUC$_{0\text{-}12}$)	-	[37]
		c.334T: 15%	Prospective, multicenter (Dominos study)	189 adult patients (France)	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	-	No association of *SLCO1B3* c.334T>G variant with AR or adverse events	[29]
		-	Retrospective (Case-Control), multicenter	284 pediatric and young adult patients (USA)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	-	No association of *SLCO1B3* c.334T>G and rs1104585 variants with leukopenia	[27]
		c.334T: 29%	Retrospective	408 adult patients (China)	MMF Cyclosporine Tacrolimus Corticosteroids 40-day follow-up	No association of *SLCO1B3* c.334T>G variant with MPA C/D (days 3-8)	-	[38]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Pharmacokinetics	Clinical outcomes	Ref.
SLCO2B1	rs2306168 (SLCO2B1*3, 1457C>T) rs2851069 (c.-71T>C)	SLCO2B1*3: 30%	Prospective	87 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No association of SLCO2B1*3 variant with MPA pharmacokinetics	No association of SLCO2B1*3 variant with diarrhea	[65]
		c.-71C: 42%	Prospective	97 adult patients (Brazil)	EC-MPS Tacrolimus Corticosteroids One-year follow-up	No association of SLCO2B1 c.-71T>C variant with MPA C/D	No association of SLCO2B1 c.-71T>C variant with DGF or AR	[24]

AcMPAG: acyl-MPA-glucuronide; AR: allograft rejection; AUC: area under the concentration-time curve; C/D: trough dose-adjusted concentration; DGF: delayed graft function; EC-MPS: enteric-coated mycophenolate sodium salt; eGFR: estimated glomerular filtration rate; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MPAG: MPA-7-O-glucuronide

confirmed by Varnell et al.[27] in a case-control study with children and young adult kidney transplant recipients. On the other hand, CYP2C8 rs11572076GG genotype was associated with reduced risk of leukopenia (GG vs. GA; OR: 0.14, 95%CI: 0.03-0.59, P = 0.008) with no association with AR, diarrhea or anemia[29]. One limiting and common aspect to these studies is the low frequency of the CYP2C8 rs11572076 variant in North American and Canadian (3%) and French (0.5%) patients[28,29]. Moreover, there is a minor involvement of CYP2C8 enzyme in MPA metabolism, which makes it difficult to interpret the findings.

In Brazilian patients on EC-MPS and tacrolimus treatment, our group showed that the CYP2C8*3 (rs11572080 + rs10509681) variant was associated with higher estimated glomerular filtration rate (eGFR), but not with AR, delayed graft function (DGF), or presence of adverse events[24,30]. The frequency of the CYP2C8*3 variant was also low (9%) in these cohorts.

UGT1A1, UGT1A7, UGT1A8, UGT1A9 and UGT2B7

Intestinal and hepatic UGTs have important roles in MPA metabolism [Figure 1]. UGT1A9 and UGT1A8 play a main role in MPAG production, and UGT2B7 and UGT1A8 in AcMPAG production, while UGT1A1, UGT1A7 and UGT1A10 plays a minor role in MPA glucuronidation[1,9,31].

The human UGT1A family (1A1, 1A3-1A10) is encoded by a single locus on chromosome band 2q37. UGT1A1 and UGT1A9 are expressed in the liver and extrahepatic tissues, where UGT1A9 is highly expressed in the kidney and shows lower expression levels in colon, adrenal and bladder[32]. UGT1A7, UGT1A8 and UGT1A10 are absent in the liver but are expressed in other tissues, such as the intestine[32]. The human UGT2 family is located on chromosome 4q13. UGT2B7 is expressed in a broad range of human tissues including liver, small intestine, and kidney[32].

UGT1A1 and UGT1A7

Given the known minimal contribution of UGT1A1, UGT1A7 and UGT1A10 to MPA metabolism, there are few pharmacogenetic studies with these isoforms.

Satoh et al.[23] investigated the influence of the UGT1A1*28 (rs3064744) variant in 30 Japanese adult patients. The authors expected to find an association between this UGT1A1 polymorphism and MPA toxicity, but they did not obtain any significant result.

Four other studies evaluated the impact of *UGT1A7* variants in kidney transplant recipients. In three cohorts, *UGT1A7* rs7586110 (-57T>G), *UGT1A7*2* and *UGT1A7*3* did not influence MPA pharmacokinetics or MMF-related gastrointestinal adverse events or leukopenia[27,33,34]. However, *UGT1A7* c.622CC (rs11692021) genotype was associated with an accumulation of MPAG (higher AUC_{0-12}) without detectable changes in MPA exposure (AUC_{0-12}) in Chinese patients[35].

UGT1A8

The variant *UGT1A8* rs1042597 (p.Ala173Gly, c.518C>G), also known as *UGT1A8*2*, is a missense variant that has a negligible role on protein activity in generating MPAG, but shows decreased production of AcMPAG[31]. Consistent with this finding, no association of *UGT1A8*2* variant with MPA or MPAG pharmacokinetics was found in kidney transplant recipients[14,36-38]. Nevertheless, in agreement with reduced enzyme activity, *UGT1A8*2* variant was associated with higher MPA AUC_{0-12}, in cyclosporine-treated patients from the FDCC Study[39], and lower MPAG AUC_{0-12} in Chinese on tacrolimus based treatment[35].

UGT1A8 rs17863762 (p.Cys277Tyr, c.830G>A, *UGT1A8*3*) is another missense variant, that also induced a reduction in the formation of MPAG *in vitro*[9,31], and did not impact MPA pharmacokinetics in pediatric or adult patients, probably because of its low frequency in the studied populations (*UGT1A8* c.830A: 1% or 2%)[39,40].

Regarding the clinical outcomes, Woillard *et al.*[34] confirmed that MMF treatment combined with tacrolimus and sirolimus increased the risk of diarrhea when compared with cyclosporine. Moreover, only in cyclosporine-treated patients, did the authors demonstrate that *UGT1A8*2* variant (c.518G allele) was associated with lower risk of MMF-related diarrhea. The supposed mechanism for this protection involved the decrease in intestinal exposure to AcMPAG[34]. It is known that local (not systemic) exposure to AcMPAG contributes to the toxicity to the intestinal mucosa[3]. However, in North American kidney transplant recipients up two weeks, *UGT1A8* c.518GG (*UGT1A8*2/*2*) genotype carriers had higher severity of gastrointestinal disorders (abdominal pain, acid reflux, indigestion, diarrhea and constipation) compared to *UGT1A8* c.518C allele carriers[41]. This finding was not confirmed in final adjusted analysis ($P = 0.069$). Woillard *et al.*[34] found that the results were not similar when they studied the relationship of *UGT1A8*2* with diarrhea alone or together with abdominal pain, nausea/vomiting and anorexia, which constituted overly heterogeneous phenotypes.

The occurrence of infections, but not diarrhea or blood disorders, was associated with high dose (2 g/day) MMF treatment and the *UGT1A8*3/*3* (c.830AA) genotype[42]. The authors suggested that this finding was due to increased MPA levels and immunosuppression, in accordance with the lower enzyme activity associated with this variant.

As described in Table 1, *UGT1A8* c.518C>G and c.830G>A variants were not associated with AR, diarrhea, leukopenia or anemia in other investigations with kidney recipients[27,29,39,43].

UGT1A9

UGT1A9 but not UGT1A8 is expressed in the liver at high levels and is considered the most important hepatic UGT enzyme involved in MPAG formation from MPA[9,32].

The variants *UGT1A9* rs6714486 (c.-275T>A) and rs17868320 (c.-2152C>T) lead to increased protein expression and activity in liver microsomes[44]. Accordingly, these polymorphisms were associated with lower MPA exposure and enterohepatic recirculation (AUC_{6-12} used as marker) in kidney patients on MPA and tacrolimus treatment[39,45,46]. Kuypers *et al.*[47] also reported this finding but only among patients treated with 2 g MMF, and van Schaik *et al.*[39] reported that the association was dependent on tacrolimus

treatment. On the contrary, in patients treated with cyclosporine or macrolides, no association with MPA or MPAG pharmacokinetics was found by others[14,40,48,49].

UGT1A9 rs2741046 (c.-331T>C), in complete linkage with rs2741045 (c.-440C>T)[44], rs10176426 (-665C>T) and rs13418420 (-1818T>C) variants in the promoter region, also showed conflicting results. In an Italian cohort treated with MMF, cyclosporine and corticosteroid-free regimen, *UGT1A9* c.-440 TT and -665CT genotypes were associated with higher MPA exposure ($AUC_{0-2, 0-4, 0-12}$ or C/D), but not with MPAG AUC_{0-12}[48]. On the contrary, *UGT1A9* c.-440CT and -1818CC genotypes were associated with higher and lower MPAG AUC_{0-12}, respectively, in Chinese patients on tacrolimus treatment[35]. Moreover, no association was found with MPA or MPAG pharmacokinetics in other studies[14,38].

The variants *UGT1A9* rs3832043 (-118delT), rs72551330 (c.98T>C) and rs2741049 (I399T>C or IVS1 + 399T>C) do not seem to influence MPA or MPAG pharmacokinetics in kidney transplant patients[14,33,35,38,40,47,49,50]. Nevertheless, higher MPA AUC_{0-12} was associated with the presence of *UGT1A9* c.98TC genotype in one study with 338 patients[39]. Although this result is in accordance with the low activity related to *UGT1A9* c.98T>C variant, the c.98C allele frequency was 2%[9,39]. Furthermore, the low frequency of the *UGT1A9* c.-275T>A, c.-2152C>T, -665C>T and c.98T>C polymorphisms was an important limitation of the investigations included in Table 1.

Regarding the clinical outcomes, many investigations showed that the *UGT1A9* c.-2152C>T, -665C>T, c.-275T>A, c.-440C>T, and c.98T>C variants were not associated with AR and MPA-related adverse events[13,22,27,29,34,47-49].

In line with the aforementioned subtherapeutic levels of immunosuppression, *UGT1A9* c.-2152C>T and c.-275T>A variants were associated with increased risk for AR (OR: 13.3, 95%CI: 1.1-162.3, $P = 0.042$)[39] in patients treated with MPA and tacrolimus. However, another investigation found that *UGT1A9* c.-275A (or c.-2152T) allele carriers had more incidence of gastrointestinal adverse events, which included diarrhea, abdominal pain, reflux, heartburn and constipation, compared to non-carriers[46]. A greater severity of diarrhea and heartburn was also associated with these variants. Moreover, the *UGT1A9* rs6744284CC genotype was associated with higher severity of constipation (Gastrointestinal Symptom Rating Scale score) at week 1 after transplantation of a North American cohort[41].

In pediatric kidney patients, *UGT1A9* c.-331C allele was associated with leukopenia[43], possibly because of increased systemic MPA exposure[48], which was speculated but not evaluated by the authors.

Pazik *et al.*[51,52] brought to light the important role of UGT1A9 in reducing exposure to dietary toxins and carcinogens. They showed that *UGT1A9* c.98TC genotype was associated with decreased graft function (proteinuria and diminished eGFR), possibly due to reduced detoxifying potential of the *UGT1A9* c.98T>C encoded enzyme.

UGT2B7

UGT2B7 is the key enzyme involved in AcMPAG formation. Djebli *et al.*[53] investigated the *in vivo* and *in vitro* effect of *UGT2B7* rs7438135 (c.-900G>A, otherwise termed c.-840G>A or c.–842G>A) and rs7439366 (802C>T) variants, which were in complete reverse linkage disequilibrium. The authors found that AcMPAG production was higher in the presence of *UGT2B7* c.-900A allele compared to c.-900GG genotype in human liver microsomes. Moreover, the same authors showed that in patients treated with sirolimus ($n = 40$), but not with calcineurin inhibitors (CNIs), *UGT2B7* c.-900AA (or 802CC) genotype was associated with higher AcMPAG AUC_{0-9} at month 1 and 3 after transplantation[53]. Likewise, no association with exposure to AcMPAG was found in other studies with adult patients treated with tacrolimus or

cyclosporine[48,54].

The effect of *UGT2B7* polymorphisms on MPA exposure in kidney recipients also was investigated. *UGT2B7* c.-900G>A and 802C>T variants had no effect on MPA pharmacokinetics in patients treated with or without corticosteroids, which may induce glucuronidation and result in low MPA exposure[36,39,49,53,55]. Baldelli *et al.*[48] found that the *UGT2B7* 802TT genotype was associated with higher MPA peak concentration without differences in AUC_{0-12} MPA. Likewise, *UGT2B7* -79G>A variant, which is linked to the 802C>T and shows a decline in the transcriptional activity of the reporter gene in Caco-2 and HepG2 cells, was not associated with MPA exposure[39,56]. On the contrary, MMF apparent oral clearance (CL/F) was significantly higher in pediatric patients with *UGT2B7* 802T allele compared to *UGT2B7* 802CC genotype carriers, early after transplantation (60 days)[40]. It is important to consider here that differences in metabolism between adults and children may modify the effect of the genetic variants[27,57].

UGT2B7 rs62298861 (IVS1 + 985A>G), rs12233719 (c.211G>T) and rs7662029 (c.-327G>A) variants were also investigated in kidney transplantation. *UGT2B7* IVS1 + 985AG and c.211GT genotypes were found to be associated with higher MPA exposure[35,50], but the association with *UGT2B7* c.211G>T was not confirmed by another study[49]. Li *et al.*[38] found an association between *UGT2B7* rs7662029 (c.-327G>A) GG genotype and a higher MPA C/D (days 3-8) in 408 Chinese treated with tacrolimus or cyclosporine, but this result was not confirmed through multiple comparison tests correction.

In a retrospective study of Brazilian adult patients, *UGT2B7* c.-900G allele was associated with prevention of AR (OR: 0.41, 95%CI: 0.19-0.92, P = 0.030)[22]. Moreover, the *UGT2B7* c.-900G allele was associated with increased risk of leukopenia (OR: 5.3, 95%CI: 1.1-25.0, P = 0.038)[27], only on treatment with non-depleting antibodies, and anemia (GA *vs.* AA, OR: 1.7, 95%CI: 1.1-2.4, P = 0.010; GG *vs.* AA, OR: 1.9, 95%CI: 1.2-2.0, P = 0.003)[29]. All these findings suggest that the *UGT2B7* c.-900G allele is associated with higher exposure to MPA, known to favor leukopenia and anemia, and decreased incidence of AR[3]. Woillard *et al.*[29] also suggested that the relationship between the *UGT2B7* c.-900 G>A variant and anemia could be because of the increased production of AcMPAG.

Another investigation failed to find an association of *UGT2B7* c.-900G>A, 802C>T and -79G>A variants with AR, diarrhea, leukopenia, or other adverse events[13,34,39,43,49,54]. Likewise, the variants rs12233719 (c.211G>T) and rs28365063 (c.372A>G) in *UGT2B7* were not associated with neutrophil count or graft function in adult patients[30,49].

ABCB1, ABCC2 and ABCG2
ABCB1, ABCC2 and ABCG2 (breast cancer resistance protein, BCRP) are expressed in tissues such as intestine, liver and kidney, consistent with their critical role in the absorption, distribution, and elimination of many drugs[58].

Wang *et al.*[18] showed that MPA is a substrate for ABCB1. MPA glucuronide metabolites are substrates for ABCC2, which is considered the main transporter of MPAG from the liver to the biliary system, although this role was suggested also for ABCG2[15]. In the kidneys, ABCC2 also seems to play an important role in MPAG excretion[19].

ABCB1
ABCB1 is located on chromosome 7, with many variants described so far. Pharmacokinetic studies of MPA have addressed the main investigated polymorphisms of *ABCB1*: rs1128503 (c.1236C>T), rs2032582 (c.2677G>T/A), and rs1045642 (c.3435C>T), which are in linkage disequilibrium[58].

In studies with kidney recipients, no association of these ABCB1 variants with exposure to MPA, and MPAG or AcMPAG were observed up to one year after transplantation[23,24,59]. Bouamar *et al.*[59] found that this result was independent of cyclosporine or tacrolimus treatment. It is known that co-administration of cyclosporine leads to lower MPA exposure, by inhibiting enterohepatic recycling of MPA, compared to co-administration of tacrolimus[3]. The inhibition of ABCC2 and OATPs by cyclosporine possibly contributes to this drug-drug interaction[18,60]. Moreover, cyclosporine is a substrate of ABCB1[25].

Satoh *et al.*[23] found that the *ABCB1* c.3435T allele was associated with greater requirement of MMF dose reduction due to diarrhea in adult patients treated with tacrolimus. Nevertheless, the authors did not find differences in dose-adjusted MPA AUC in *ABCB1* c.3435T allele carriers compared to c.3435CC genotype individuals. Thus, they speculated that the interaction of ABCB1 with other transporters and enzymes might be involved in MPA-induced gastrointestinal toxicity in their small sample size (n = 30)[23]. *ABCB1* c.3435TT genotype may decrease protein expression or activity, leading to increased drug absorption across the intestine and its higher systemic and intracellular concentrations[61].

On the other hand, in a study with 237 Caucasian patients on MMF and cyclosporine treatment, the *ABCB1* c.2677T allele and c.3435T/c.2677T/c.1236T was associated haplotype with increased risk of AR (OR: 3.2, 95%CI: 1.5-6.7, P = 0.003 and OR: 2.1, 95%CI: 1.3-3.4, P = 0.002; respectively), but MPA pharmacokinetic data were unavailable[25]. Since low MPA AUC_{0-12} was associated with increased incidence of biopsy-proven acute rejection[3], this result from Grinyó *et al.*[25] collaborates the complex mechanisms of clinical outcomes in immunosuppressive therapy.

Other investigations found no association of *ABCB1* c.1236C>T, c.2677G>T/A, and c.3435C>T variants with AR, DGF, diarrhea, leukopenia or other MPA-related adverse events in pediatric or adult kidney recipients[13,24,26,27,59].

ABCC2
The extensively studied variant of *ABCC2* (on chromosome 10), the rs717620 (c.-24C>T), is located in the 5´-UTR. The effect of this polymorphism in several *in vivo* studies is contradictory, suggesting that it is highly tissue specific and dependent on regulatory factors, such as the epigenetics (miRNA expression)[58]. Naesens *et al.*[62] investigated the *ABCC2* c.-24C>T variant, in linkage disequilibrium with rs3740066 (c.3972C>T), in adult kidney transplant recipients treated with MMF and tacrolimus for one year. At day 7, only non-carriers of the *ABCC2* c.-24C>T variant and patients with mild liver dysfunction had significantly lower MPA exposure than those without liver disease. This difference was not observed in *ABCC2* c.-24T allele carriers. The reasons were not clarified. In the same study, from day 42 post-transplantation, the *ABCC2* c.-24T allele was associated with higher MPA C/D and AUC[62]. The authors suggested that the variant was associated with increased protein expression and/or activity and enhanced enterohepatic recirculation. In line with this, the *ABCC2* c.-24TT genotype was also associated with higher MPA C/D (days 3-8) in 408 Chinese patients on cyclosporine or tacrolimus treatment, but this result was not confirmed after Bonferroni correction in the multiple comparisons analysis[38].

van Schaik *et al.*[39] found that MPA AUC_{0-12} was 17%-23% higher for *ABCC2* c.-24C>T carriers, but this difference reached statistical significance only at 6 weeks post-transplantation. Conversely, the *ABCC2* c.-24T allele was associated with a lower MPA AUC at month 1, in a study with 55 kidney transplant recipients on tacrolimus and sirolimus therapy[63].

Božina *et al.*[64] did not find any association between the *ABCC2* c.-24T variant and MPA pharmacokinetics in kidney recipient or donors, but the A allele of the *ABCC2* rs2273697 (Val417Ile, c.1249G>A) in kidney donors was associated with a reduced peak (29%) and early (AUC_{0-2}, 33%) exposure to MPA, suggesting

an increased renal elimination. Moreover, the authors showed that the combination of cyclosporine and *ABCC2* c.1249A allele reduced MPA AUC_{0-2} by 49%, an additive effect of this immunosuppressant.

Lack of association of *ABCC2* c.-24C>T, 1249G>A, c.3972C>T, and rs8187694 (3563T>A) variants with MPA or MPAG pharmacokinetics was reported by other studies[14,24,37,39,40,45,48,49,65,66].

Regarding clinical outcomes, Naesens *et al.*[62] found that *ABCC2* c.-24T allele carriers had more frequent episodes of diarrhea that non-carriers in the first year after transplantation. The authors considered the limitation of the sample size but stated that an increased enterohepatic recirculation of MPAG associated with the *ABCC2* c.-24C>T variant could lead to diarrhea. It is important to mention that the local exposure and not the systemic concentration of MPA is relevant for gastrointestinal adverse events. Moreover, AcMPAG, produced in gastrointestinal cells and also substrate of ABCC2, contributes to cell toxicity[3,15].

Other studies failed to confirm associations between *ABCC2* polymorphisms and clinical outcomes (AR, DGF, graft function) or MPA-related adverse events in pediatric or adult kidney recipients[13,22,24,25,27,29,30,34,39,49,65].

ABCG2
Brazilian, Chinese, and North American cohorts have been studied regarding two *ABCG2* variants in pediatric and adult kidney transplant patients [Table 2]. The *ABCG2* c.421C>A (rs2231142) variant leads to the amino acid exchange Gln141Lys, whereas *ABCG2* -20 + 11790G>A (rs4491984) is an intronic polymorphism.

The investigations pointed out that these variants did not influence MPA or MPAG exposure or clinical outcomes during treatment with different immunosuppressive therapies[24,27,30,37,38].

SLCO1B1, SLCO1B3 and SLCO2B1
OATPs additionally contribute to drug disposition, with ABC proteins; however, OATPs do not depend directly on using cellular ATP[67,68]. OATP1B1 and OATP1B3 are mainly expressed in the liver, while OATP1A2 is expressed in the intestine, biliary cells of the liver, and distal nephron of the kidney[67].

In studies with OATP-transfected human embryonic kidney (HEK) cells, MPAG uptake, but not MPA, was enhanced by OATP1B3 (*SLCO1B3*) and to a lesser extent by OATP1B1 (*SLCO1B1*). MPA or MPAG uptake was not influenced by OATP1A2 (*SLCO1A2*)[14]. In line with this, Michelon *et al.*[13] found that MPAG and AcMPAG, but not MPA, were substrates of OATP1B1.

SLCO1B1
A large number of *SLCO1B1* variants have been described. The two *SLCO1B1* common variants rs2306283 (p.Asn130Asp, c.388A>G) and rs4149056 (p.Val174Ala, c.521T>C) form together four distinct haplotypes: *SLCO1B1*1A* (c.388A-c.521T, reference haplotype), *1B* (c.388G-c.521T), *5* (c.388A-c.521C) and *15* (c.388G-c.521C)[69].

Kidney transplantation with macrolide or cyclosporine-based treatment has shown no association between the *SLCO1B1* c.388A>G, c.521T>C, and rs11045819 (463C>A) variants or haplotypes with MPA, MPAG or AcMPAG pharmacokinetics[14,24,49,59,65].

Likewise, *SLCO1B1* variants have not been associated with AR, DGF, diarrhea, leukopenia or neutrophil count in the studies summarized in Table 2[22,24,27,49,59,65]. Nevertheless, *SLCO1B1* c.521C allele (*SLCO1B1*5*) was associated with reduced MPA-related adverse events, including leukopenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting or infection in French patients on cyclosporine-free treatment[13]. Possibly

because cyclosporine inhibits OATP1B1, the effect of the *SLCO1B1* c.521C allele was not detectable in the therapy with this immunosuppressant[13,60]. Indeed, cyclosporine-based treatment and *SLCO1B1* c.521C allele were independent factors related to risk reduction of adverse events (OR: 0.22, 95%CI: 0.08-0.56, *P* = 0.002 and OR: 0.38, 95%CI: 0.21-0.69, *P* = 0.001; respectively)[13]. It was also demonstrated *in vitro* the reduced uptake of MPAG and AcMPAG related to *SLCO1B1* c.521C variant. The authors hypothesized that carriers of the *SLCO1B1* c.521C allele had impaired hepatic uptake of MPAG and AcMPAG, which leads to less enterohepatic recycling and, consequently, reduced exposure to MPA and less adverse events[13]. However, this study did not evaluate MPA exposure, and other investigations did not find an association between the *SLCO1B1* c.521T>C variant and MPA pharmacokinetics, as previously mentioned.

SLCO1B3
Four variants in *SLCO1B3* were investigated in pediatric and adult recipients of kidney transplantation [Table 2]. Three are missense variants, *SLCO1B3* rs4149117 (Ser112Ala, c.334T>G), rs7311358 (Met233Ile, c.699G>A) and rs60140950 (Gly256Ala, c.767G>C).

SLCO1B3 c.334T>G and c.699G>A are in linkage disequilibrium, and the *SLCO1B3* c.334G-c.699A haplotype was associated with reduced MPAG uptake in HEK293 cells *in vitro*[14]. In a study with 70 patients on tacrolimus and sirolimus treatment, but not on cyclosporine, the *SLCO1B3* c.334GG genotype was associated with lower MPA peak concentration and exposure (AUC_{0-12}) and higher MPAG/MPA ratio[14]. On the basis of *in vitro* and *in vivo* results, the authors suggested that reduced OATP1B3 activity would decrease hepatic uptake of MPAG, reducing reabsorption of MPA through enterohepatic cycling in *SLCO1B3* c.334GG genotype carriers.

Other investigations did not find an association between *SLCO1B3* c.334T>G (or c.699G>A) variant and exposure to MPA, MPAG, or AcMPAG during treatment with either cyclosporine, in line with the previous findings[14], or tacrolimus[37,38,59]. On the contrary, the *SLCO1B3* c.334GG (699AA) genotype was associated with higher MPA AUC_{6-12}, considered a marker of MPA recirculation, in Japanese patients with tacrolimus-based therapy at day 28 after transplantation[65].

SLCO1B3 c.334T>G (or 699G>A) and rs1104585 variants were not associated with AR, leukopenia, diarrhea or other adverse events[13,27,29,59,65].

SLCO2B1
In Brazilian or Japanese kidney recipients, early or long after transplantation, *SLCO2B1* c.-71T>C (rs2851069) and *SLCO2B1*3* (rs2306168) variants did not influence MPA pharmacokinetics or clinical outcomes of tacrolimus based-therapy[24,65].

GENES RELATED TO MPA PHARMACODYNAMICS

Polymorphisms in *IMPDH1* or *IMPDH2* that result in increased IMPDH activity are likely to enhance T and B cell proliferation and decrease the response to MPA in kidney transplantation[1,2]. As a result, less sensitivity to MPA requires an increase in the dose of MMF to avoid the risk of acute rejection, but this clinical approach exposes patients to higher blood concentrations of MPA and increases the likelihood of adverse events[1].

The pharmacogenomics studies involving genes related to MPA pharmacodynamics are summarized in the Table 3.

IMPDH1

A large-scale genomic study investigated variants in *IMPDH1* using a gene resequencing approach. It identified 73 variants (59 novel) in a cohort of 288 healthy subjects, including four missense variants:

rs72624960 (Ser275Leu), rs72624961 (Ala285Th), rs61751223 (His296Arg), and rs72624967 (Arg412Trp). Functional analysis revealed that *IMPDH1* Leu275 significantly reduced enzyme activity, where structural analysis predicted that the amino acid substitution alters the structure and function of the enzyme[70]. The authors also identified two variants previously described in *IMPDH1*: the synonymous variant rs2228075 (Ala525Ala, c.1320G>A, C>T) and the intronic variants rs2278293 (c.579 + 119G>A, C>T) and rs2278294 (c.580-106G>A, C>T).

The *IMPDH1* rs2278293 and rs2278294 (intronic) and rs2228075 (synonymous) variants were investigated in kidney recipients from several populations treated with MMF [Table 3].

Wang *et al.*[71] examined the contribution of 17 variants in *IMPDH1*, including rs2228075, rs2278293 and rs2278294, to acute rejection or toxicity in 191 adult kidney recipients from the US on MMF therapy. The rs2278293 A allele (OR: 0.34, 95%CI:0.15-0.76, P = 0.008) and the rs2278294 A allele (OR: 0.40, 95%CI: 0.18-0.89, P = 0.02) were associated with reduced risk for acute rejection (AR) in the first postoperative year[71]. Gensburger *et al.*[72] also explored the influence of both *IMPDH1* intronic polymorphisms on clinical outcomes, in 456 kidney recipients from the Apomygree and FDCC studies, and found an association of the rs2278294 A allele with reduced AR risk (OR: 0.54, 95%CI: 0.34-0.85, P = 0.0075), suggesting a protective effect of this variant.

Other studies reported a lack of association of both *IMPDH1* rs2278293 and rs2278294 variants with AR in adult patients from the Transgene Study[13] and the Collaborative Transplant Study (the largest cohort, over 1000 kidney recipients) on MMF treatment[73]. Similar results were also found in adult kidney recipients treated with EC-MPS from the multicenter Dominos study[29]. The *IMPDH1* rs2278293 was also not associated with AR in a kidney transplantation study from Brazil[22].

Shah *et al.*[73] reported the lack of an association of the variants rs2278293 and rs2278294 in *IMPDH1* with MMF long-term dose tolerated and dose achieved in adult kidney recipients from the Collaborative Transplant Study. A short-term follow-up study also reported no direct association of both *IMPDH1* rs2278294 and rs2278293 polymorphisms with subclinical AR in 82 Japanese adult kidney recipients. However, the interaction of the rs2278293 A allele with high MPA night-time exposure range (AUC > 60 μg.h/mL and $C_0 \geq 1.9$ μg/mL) increased the risk of subclinical AR[74].

Two studies investigated the missense variant *IMPDH1* rs2228075 (Ala525Ala, c.1320G>A) and the risk for AR, though no significant association was found in MMF-treated adult kidney recipients from the US[71] and from the CAESAR Study[25]

The Collaborative Transplant Study explored the variants *IMPDH1* rs2278293 and rs2278294 in a large cohort of kidney recipients, and found no association with long-term graft function (one year) and graft survival (five years)[73].

The influence of *IMPDH1* variants on hematological and gastrointestinal adverse events related to MMF therapy was also explored in several studies. The *IMPDH1* rs2278294 G>A was reported to be associated with increased risk of leukopenia (A allele: OR: 1.66, 95%CI: 1.11-2.48, P = 0.0139) in adult kidney recipients from the Apomygree and FDCC studies[72]. Moreover *IMPDH1* rs2278294 G and rs2228075 G alleles were associated with delayed time to leukopenia in children and young adult patients from USA[27]. Although these intronic variants were predicted not to affect IMPDH1 function, the authors suggested that these alleles may affect the sensitivity of the enzyme to MPA.

Other studies reported lack of association of *IMPDH1* rs2278293, rs2278294 or rs2228075 with leukopenia in adult kidney recipients on MMF therapy from the US[71], Apomygre and FDCC studies[72], and Transgene

Table 3. Genes related to mycophenolic acid pharmacodynamics in kidney transplantation

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Clinical outcomes	Ref.
IMPDH1	rs2228075 C>T (Ala525Ala, c.1320G>A)	c.1320A: 22%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	No association of *IMPDH1* rs2228075 variant with AR	[25]
	rs2278293 C>T (c.579+119G>A) rs2278294 C>T (c.580-106G>A)	rs2278293 A: 46% rs2278294 A: 36%	Prospective, multicenter (Apomygre and FDCC studies)	456 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	*IMPDH1* rs2278294 A allele was associated with reduced risk of AR and increased risk of leukopenia No association of rs2278293 with AR, leukopenia, CMV and other infections	[72]
		rs2278293 A: 44% rs2278294 A: 45%	Prospective	82 adult patients (Japan)	MMF Tacrolimus Corticosteroids At day 28	No direct association of *IMPDH1* variants with subclinical AR. *IMPDH1* rs2278293 A allele combined with high MPA night-time exposure range (AUC > 60 μg.h/mL and C_0 U 1.9 μg/mL) was associated with subclinical AR	[74]
		rs2278293 A: 49% rs2278294 A: 38%	Retrospective (Transgene study)	218 adult patients (France)	MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up	No association of *IMPDH1* variants with MPA-related AR or leukopenia	[13]
		rs2228075 T: 25% rs2278293 A: 43% rs2278294 A: 40%	Retrospective	191 adult patients (USA)	MMF Tacrolimus Prednisone One-year follow-up	The variants *IMPDH1* rs2278293 and rs2278294 were associated with reduced risk of AR No association of *IMPDH1* variants with leukopenia	[71]
		rs2278293 T: 45% rs2278294 A: 40%	Prospective, multicenter (Collaborative Transplant study)	1,040 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *IMPDH1* variants with MMF doses tolerated (1 year) and dose achieved (3 years) No association of *IMPDH1* variants with AR, graft function (1 year) or graft survival (5 years)	[73]
		rs2278923 T: 47% rs2278924 T: 33%	Prospective, multicenter (Dominos study)	189 adult patients	EC-MPS, Cyclosporine Corticosteroids Six-month follow-up	No association of *IMPDH1* variants with AR, leukopenia anemia or diarrhea	[29]
		rs2228075: - rs2278293: - rs2278294: -	Retrospective (Case-control), multicenter	284 pediatric and young adult patients (USA)	MMF Tacrolimus Cyclosporine Sirolimus Corticosteroids One-year follow-up	*IMPDH1* rs2228075 G and rs2278294 G alleles were associated with increased time to leukopenia	[27]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Clinical outcomes	Ref.
		rs2278293 A: 47%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	No association of *IMPDH1* variant with AR	[22]
		rs2278293 A: 45% rs2278294 A: 30%	Prospective	190 adult patients (Poland)	MMF Cyclosporine Tacrolimus Corticosteroids Five-year follow-up	*IMPDH1* rs2278294 G allele was associated with slower BMI gain	[75]
IMPDH2	rs11706052 A>G (c.819+10T>C, also known as 3757T>C)	3757C: 7%	Prospective, multicenter (CAESAR study)	237 adult patients	MMF Cyclosporine Corticosteroids One-year follow-up	*IMPDH2* 3757C allele was associated with increased risk of AR	[25]
	rs121434586 (Leu236Phe, c.787C>T)	3757TC+CC: 9% c.787T: 0.3%	Retrospective	191 adult patients (USA)	MMF Tacrolimus Prednisone One-year follow-up	No association of *IMPDH2* variants with AR or leukopenia	[71]
	rs4974081 (-3624A>G)	3757C: 7%	Prospective	101 adult patients (Netherlands)	MMF Tacrolimus Corticosteroids One-year follow-up	*IMPDH2* 3757C allele was associated with increased MPA plasma concentration (6 h after MMF intake) and increased IMPDH activity in PBMC (12 h after MMF intake) No association of *IMPDH2* variant with AR	[78]
		rs11706052 C: 9% rs4974081 G: 24%	Prospective (Apomygre and FDCC studies)	456 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of the *IMPDH2* rs11706052, rs4974081 variants with AR, leukopenia or CMV infection	[72]
		3757C: 8%	Prospective	177 adult patients (Poland)	MMF Calcineurin inhibitors Corticosteroids One-year follow-up	*IMPDH2* 3757 C allele was associated with increased lymphocyte counts and reduced risk of lymphopenia No association of *IMPDH2* variant with AR, neutropenia, gastrointestinal adverse events or serious infections	[80]
		rs11706052 G: 19%	Prospective, multicenter (Collaborative Transplant study)	1,040 adult patients	MMF Cyclosporine Tacrolimus Corticosteroids One-year follow-up	No association of *IMPDH2* variant with MMF doses tolerated (1-year) and dose achieved (3-years) No association of *IMPDH2* variant with AR, graft function (1 year) or survival (5 years)	[73]
		rs11706052 C: 11%	Prospective, multicenter (Dominos study)	189 adult patients	EC-MPS Cyclosporine Corticosteroids Six-month follow-up	No association of *IMPDH2* variant with AR, leukopenia, anemia or diarrhea	[29]

Gene	Variant	Allele frequency	Study design	Population	Immunosuppressive regimen	Clinical outcomes	Ref.
		rs11706052 C: - rs4974081 G: -	Retrospective (Case-control), multicenter	284 pediatric and young adult patients (USA)	MMF Tacrolimus Cyclosporine Sirolimus Corticosteroids One-year follow-up	No association of *IMPDH2* variants with leukopenia or time to leukopenia	[27]
		rs11706052 C: 11%	Retrospective (Case-control)	145 adult patients (Brazil)	MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up	*IMPDH2* rs11706052 C allele was associated with reduced risk of AR	[22]
		rs11706052 C: 8%	Prospective	190 adult patients (Poland)	MMF Cyclosporine Tacrolimus Corticosteroids Five-year follow-up	No association of *IMPDH2* variant with BMI change	[75]

AR: acute rejection; AUC: area under the concentration-time curve; BMI: body mass index; CMV cytomegalovirus; EC-MPS: enteric-coated mycophenolate sodium; MMF: mycophenolate mofetil; MPA: mycophenolyc acid

Study[13]. Likewise both rs2278294 and rs2278293 polymorphisms were not associated with leukopenia or anemia in adult patients from the Dominos Study within six months of EC-MPS treatment[29]. Eight other variants in *IMPDH1* were also identified by Wang *et al.*[71], but no association with leukopenia was found.

Woillard *et al.*[29] also investigated the influence of *IMPDH1* rs2278923 and rs2278924 polymorphisms on gastrointestinal adverse events, such as diarrhea, but no association was found in adult kidney recipients from Dominos Study on EC-MPS therapy. Likewise, no association was found between these variants and susceptibility to CMV and other infections in adult kidney recipients on MMF therapy from the Apomygre and FDCC studies[72].

Pazik *et al.*[75] explored the influence of *IMPDH1* rs2278923 and rs2278924 on time-dependent change in body mass index (BMI) of adult kidney recipients from Poland, and found an association of the rs2278294 G allele with slower BMI gain over five years post-transplantation.

IMPDH2

Wu *et al.*[70] identified 25 variants (24 novel) in *IMPDH2*, including the missense rs72624919 (Ser485Cys), in 288 healthy subjects. The functional analysis was carried out with Ser485Cys and Leu263Phe (rs121434586, c.787C>T), a missense variant previously described[76]. The *IMPDH2* Phe263, but not the Cys485, reduced markedly protein level and enzymatic activity, and altered the structure and function of the enzyme. They also detected the intronic variant *IMPDH2* rs72639214 (IVS1-93), which was associated with reduced *IMPDH2* basal mRNA expression in lymphoblastoid cell lines, as well as the intronic variant *IMPDH2* rs11706052 A>G (c.819 + 10T>C) also known as 3757T>C[70].

Ten studies explored the *IMPDH2* rs121434586 (Leu263Phe), rs11706052 (intronic) and rs4974081 (-3624 A>G), a 5′upstream variant which was predicted to be a potential transcription factor binding site[77], in MMF-treated kidney recipients from various cohorts [Table 3].

The *IMPDH2* rs11706052 (3757T>C) was found to be associated with increased IMPDH activity in PBMC and increased IMPDH plasma concentration, six and 12 h, respectively, after MMF oral intake by 101 adult kidney recipients[78]. In this line of evidence, Winnicki *et al.*[79] reported that *IMPDH2* 3757T>C reduced the antiproliferative effect of MPA on lymphocytes (50% inhibition) isolated from 20 healthy volunteers. The authors suggested that this variant is associated with a poor response to MPA therapy. However, in a large cohort from the Collaborative Transplant Study, the *IMPDH2* rs11706052 had no impact on MMF dose tolerated (one year) or dose achieved (three years)[73].

IMPDH2 rs11706052 (3757T>C) was also found to be associated with increased risk of AR at one year (3757C allele: OR: 3.39, 95%CI: 1.42-8.09, $P = 0.006$) in adult kidney recipients treated with MMF from the CAESAR study[25]. Conversely, the rs11706052 was reported to reduce the risk of AR (3757C allele: OR: 0.24, 95%CI: 0.07-0.78, $P = 0.018$) in Brazilian adult patients[22].

Further studies did not confirm the association of the *IMPDH2* rs11706052 with AR in adult patients from different populations[29,71,78,80], including large cohorts[72,73], and pediatric patients[27]. Lack of association with AR was also described for *IMPDH2* variants rs121434586 (Leu236Phe, c.787C>T) and rs4974081 (-3624A>G) in adult kidney recipients on MMF treatment from a US cohort[71] and the Apomygre and FDCC studies[72].

Shah *et al.*[73] also reported the lack of an association of the *IMPDH2* rs11706052 with long-term graft function (one year) and graft survival (five years) in a large cohort of kidney recipients on MMF therapy from the Collaborative Transplant Study.

Some studies also explored the influence of polymorphisms in *IMPDH2* on adverse events related to MPA. Pazik *et al.*[80] described an association of the *IMPDH2* rs11706052 (3757T>C) polymorphism with increased lymphocyte counts and reduced risk of lymphopenia (3757C allele: OR: 0.32, 95%CI: 0.11-0.90, $P = 0.032$), but not with neutropenia in adult kidney recipients from Poland. Other studies did not confirm the influence of the rs11706052 variant on leukopenia in adult kidney recipients on MMF[71,72] or EC-MPS treatment[29]. In the same way, a retrospective study reported no association of rs11706052 with leukopenia or time to leukopenia in children and young adults from the US[27].

Other variants in *IMPDH2*, such as rs121434586 (Leu236Phe, c.787C>T) and rs4974081 (-3624A>G), were studied, but no association with leukopenia was found in adult patients[71,72], children, and young adults[27] on MMF treatment. The influence of the *IMPDH2* rs11706052 on anemia was also explored but no association was found in adult patients from the Dominos Study on EC-MPS therapy[29].

Two studies explored MPA-related gastrointestinal adverse events and found no association of *IMPDH2* rs11706052 with diarrhea in adult patients on MMF[80] or EC-MPS treatment[29].

Gensburger *et al.*[72] found a lack of association between *IMPDH2* rs11706052 and rs4974081 and the susceptibility to CMV and other infections in adult kidney recipients on MMF therapy from the Apomygre and FDCC studies. This was also reported for *IMPDH2* rs11706052 and the incidence of serious infections in adult patients on MMF treatment from Poland[80]. Pazik *et al.*[75] also studied how the presence of *IMPDH2* rs11706052 could change the BMI of adult kidney recipients on MMF treatment in a time-dependent manner, but no association was found with BMI change over five years post-transplantation.

CLINICAL IMPLEMENTATION

Increasing knowledge in pharmacogenomics and its clinical implementations depend on several factors, including the robustness of the studies, sample size, and reproducibility of the results in different populations. The Pharmacogenomics Knowledge Base (PharmGKB; www.pharmgkb.org) aims to collect, encode and disseminate understanding of human genetic variations on drug responses[81,82], and most of the existing pharmacogenetic information is compiled in this database[83]. For clinical annotations, PharmGKB curators determine "levels of evidence" score that is a measure of confidence in the variant-drug associations using well-defined criteria based on careful literature review. This score has four levels, from 1 to 4 (1A, 1B, 2A, 2B, 3 and 4), 1A being the highest scientific evidence[81,82].

In kidney transplantation, the clinical annotations registered in PharmGKB include the following variants implicated in MPA efficacy, metabolism or toxicity: *IMPDH1* rs2278293[13,71-74] and rs2278294[13,71-74], *IMPDH2* rs11706052[25,72,73,78-80], *ABCB1* rs2032582[25], *ABCC2* rs2273697[64,83], rs3740066[83], and rs717620[64], *CYP2C8* rs11572076[29], *UGT1A8* rs1042597[34], *UGT1A9* rs3832043[83,84], rs6714486[34,47,51], rs17868320[47,51], and rs72551330[51], *UGT2B7* rs7438135[29], *SLCO1B1* rs4149056[13,59] and rs2306283[83], and *SLCO1B3* rs7311358[14,65] and rs4149117[13,14,59,65]. All these variants are assigned as evidence level 3 with exception of *SLCO1B3* rs4149117, which is level 4. Level 3 means "a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association", whereas level 4 is based on "a case report; on a study that did not achieve significance but is biologically plausible; or on *in vitro*, molecular, or functional assay evidence"[81,82].

Although the data reviewed here highlight the importance of pharmacogenomics in the variability of the response to MPA, these clinical associations are not strong enough to be used for clinical translation[85] and more evidence is needed to clarify the level of contribution of pharmacogenomics in kidney transplant patients treated with MPA.

Moreover, it is important to mention that three regulatory agencies, Food and Drug Administration (FDA, US), Pharmaceuticals and Medical Devices Agency (PMDA, Japan) and Health Canada (Santé, Canada) (HCSC), recommend drug labeling for MPA as an "actionable PGx" (genetic testing not required) for patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase, such as Lesch-Nyhan and Kelley-Seegmiller syndrome, because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid[81,82,86].

FINAL CONSIDERATIONS

The genotype-phenotype associations reviewed here showed that genetic influence on MPA treatment seems to be small, especially due to inconsistency between studies. However, many factors need to be considered.

The strategies applied to MPA dosing were different between studies, which included fixed dosing ("one-dose-fits-all") and dosing to a therapeutic range (therapeutic drug monitoring-TDM). MPA AUC_{0-12} has been recommended as the best marker for dose adjustment[87]. However, unlike other drugs such as tacrolimus, MPA trough level showed a poor correlation with AUC[87-89]. TDM use for MPA is drawing much attention, but it is still controversial[3]. It is known that TDM can contribute to correct the variability in MPA exposure[89,90]. Therefore, TDM of MPA can minimize the genetic influence on the efficacy and safety of therapy.

Moreover, the studies included in this review are heterogeneous in some aspects, such as population (sample size, ethnics, age, *etc.*), inherent characteristics of the clinical approach, immunosuppressive scheme and

follow-up time, time after transplantation, definition of the analyzed events (for example, AR, DGF or adverse events), and analytical methods for measurement of the MPA exposure.

Together, these heterogeneities demonstrate the limitations of this review for pointing out the pharmacogenetic biomarkers useful for clinical applications of MPA in kidney transplantation.

CONCLUSION

Individualized treatment can contribute to improve efficacy and decrease the toxicity of immunosuppressive drugs. Here, the influence of genetic variants on MPA pharmacokinetics and pharmacodynamics in kidney transplant recipients was reviewed. The combination of multiple drugs, the different sample sizes, and the lack of association consistency between studies have been important challenges of MPA pharmacogenomics. Together they limit the conclusions and clinical applications of MPA pharmacogenomics in kidney transplantation. Currently, further pharmacogenomic studies are needed to elucidate the contribution of genetic background to the effectiveness and safety of MPA therapy.

DECLARATIONS

Authors' contributions
Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Genvigir FDV, Cerda A, Hirata RDC
Prepared the figure and critically reviewed the manuscript: Hirata TDC, Hirata MH

Availability of data and materials
Not applicable.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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