Mycophenolic acid pharmacogenomics in kidney transplantation

Fabiana Dalla Vecchia Genvigir¹, Alvaro Cerda², Thiago Dominguez Crespo Hirata¹, Mario Hiroyuki Hirata¹, Rosario Dominguez Crespo Hirata¹

¹Department of Clinical and Toxicological Analyses, School of Pharmaceutical Sciences, University of Sao Paulo, Sao Paulo 05508-000, Brazil.
²Department 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

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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, hematomal 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.

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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 acylglucuronide 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\(^18\).
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. MPA is also eliminated in the urine as MPA in negligible amounts, and mostly as MPAG, possibly mediated by ABCC2.
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 [24], 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 [22-24].

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]     |
|               | rs3890213 (-1548A>G)     | -                | Prospective         | 80 adult patients (Japan)  | MMF                        | Tacrolimus Corticosteroids             | No association of CES2 -1548A>G, 4595A>G and 8721C>T variants with MPA pharmacokinetics | [21]     |
|               | rs2303218 (4595A>G)      | -                | Prospective         | 145 adult patients (Brazil) | MMF                        | Cyclosporine Tacrolimus Sirolimus Corticosteroids | No association of CES1 356C>T variant with AR       | [22]     |
|               | rs2241409 (8721C>T)      | 8721T: 22%       | Retrospective (Case-control) | 145 adult patients (Brazil) | MMF                        | Cyclosporine Tacrolimus Sirolimus Corticosteroids | No association of CES2 -1548A>G, 4595A>G and 8721C>T variants with AR or diarrhea | [21]     |
| CYP2C8        | rs11572076 G>A           | -                | Retrospective (Case-control), multicenter | 284 pediatric and young adult patients (USA) | MMF                        | Cyclosporine Tacrolimus Sirolimus Corticosteroids | 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 | No association of CYP2C8 rs11572076 variant with leukopenia | [29]     |
| CYP2C8*3      | [rs11572080 (c.416G>A) + rs10509681 (c.1196A>G)] | CYP2C8*3: 9%     | Prospective, multicenter | 148 adult patients (Brazil) | EC-MPS                     | Sacrolimus 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%               | -                | Prospective         | 97 adult patients (Brazil) | EC-MPS                     | Tacrolimus Corticosteroid One-year follow-up | No association of CYP2C8*3 variant with MPA C/D       | [24]     |
|               | c.1196G:10%             | -                | Prospective         | 97 adult patients (Brazil) | EC-MPS                     | Tacrolimus Corticosteroid One-year follow-up | No association of CYP2C8*3 variant with AR       | [24]     |

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| Gene Variant          | Allele frequency | Study design | Population | Immunosuppressive regimen | Pharmacokinetics | Clinical outcomes | Ref. |
|----------------------|------------------|--------------|------------|----------------------------|------------------|-------------------|------|
| CYP3A4 rs2740574 (CYP3A4*1B, -392G: 5%) | Prospective, multicenter (CAESAR study) | 237 adult patients | MMF Cyclosporine Corticosteroids One-year follow-up | - | No association of CYP3A4*1B 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 AUC0-12 | 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 | - | 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] |
| - Retroactive (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 daytime and nighttime MPA AUC0-12 | No association of CYP3A5*3 variant with AR or gastrointestinal adverse events | | [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 AUC0-12 | No association of UGT1A1*28 variant with AR or gastrointestinal adverse events | | [23] |
| Gene     | Variant | Allele frequency | Study design                        | Population                  | Immunosuppressive regimen | Pharmacokinetics | Clinical outcomes                                                                 | Ref.  |
|----------|---------|------------------|-------------------------------------|-----------------------------|----------------------------|-------------------|------------------------------------------------------------------------------------|-------|
| UGT1A7   | rs7586110 (-57T>G) | -                | Retrospective (Case-Control), multicenter | 284 pediatric and young adult patients (USA) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | -                | No association of UGT1A7 -57T>G variant with leukopenia                            | [27]  |
|          | rs1692021 (c.622T>C) | UGT1A7*2: 8% UGT1A7*3: 28% | Prospective                          | 80 adult patients (Japan)   | MMF Tacrolimus Corticosteroids | -                | No association of UGT1A7*2 and UGT1A7*3 variants with MPA pharmacokinetics         | [33]  |
|          | rs178683324 (c.622C>G) | c.622: 37%       | Retrospective                        | 256 adult patients (France) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | -                | No association of UGT1A7 c.622C>T variant with gastrointestinal adverse events | [34]  |
|          | UGT1A7*3 (c.397T>G + c.401C>A) | UGT1A7*2: 8% UGT1A7*3: 28%        | Prospective                          | 127 adult patients (China)  | MMF Tacrolimus Corticosteroids | UGT1A7 c.622CC >c.622CC< genotype was associated with higher exposure to MPAG (AUC<sub>0-12</sub>) | -     |
| UGT1A8   | rs17863762 (UGT1A8*3, c.830G>A) | -                | Retrospective                        | 74 adult patients (Brazil)  | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | -                | Treatment with MMF 2 g/d and UGT1A8*3 c.830G>A genotype were associated with occurrence of infections, but not diarrhea, or blood disorders | [42]  |
|          | rs1042597 (UGT1A8*2, c.518C>G) | UGT1A8*2: 58%    | Prospective                          | 72 adult patients (Japan)   | MMF Tacrolimus Corticosteroids | -                | 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 Sirolimus 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 Sirolimus Corticosteroids | UGT1A8*2/c.518G A genotype was associated with higher MPA AUC<sub>0-12</sub> in cyclosporine-treated patients | [39]  |
|          | c.518G: 26% |                   | Prospective (included multicenter Apomygre study) | 185 patients (France)       | MMF Cyclosporine Sirolimus Corticosteroids | UGT1A8*2/c.518G A variant with MPA or MPAG pharmacokinetics | -     |  |
| 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                       | -               | 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                       | No association of UGT1A8 c.830A>G variant with MPA pharmacokinetics               | [40] |
| c.518G: 43% |         |                 | Prospective, Multicenter      | 37 adult patients (China)         | MMF                       | No association of UGT1A8 c.518G variant with MPA or MPAG exposure (AUC<sub>4-12</sub> or AUC<sub>0-12</sub>) | [37] |
| c.518G: 32% |         |                 | Prospective                   | 109 adult patients (USA)          | MMF EC-MPS Cyclosporine Tacrolimus Corticosteroids | -               | 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) | MMF EC-MPS Cyclosporine Tacrolimus Corticosteroids | - | 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<sub>0-12</sub> | [35] |
|             |         |                 | Retrospective (Case-Control), multicenter | 284 pediatric and young adult patients (USA) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | - | No association of UGT1A8*2 and UGT1A8*3 variants with leukopenia | [27] |
| c.518G: 49% |         |                 | Retrospective                 | 408 adult patients (China)        | MMF Cyclosporine Tacrolimus Corticosteroids | 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) | 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<sub>0-12</sub> and AUC<sub>6-12</sub> 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] |
|       | rs6731242 (-1887T>G) | c.-1887T: 13% -665T: 4% -440/-331T/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<sub>0-2, 0-4, 0-12</sub>) | No association of UGT1A9 c.-440C>T (or c.-331T>C) variant with gastrointestinal adverse events | [48] |
|       | rs13418420 (-1818T>C) | c.-2152T: 1% c.-1887T: 13% -665T: 4% -440/-331T/C: 41% c.-275A: 5% c.98C: 0% | Mixed | 38 pediatric patients (USA) | MMF Tacrolimus Corticosteroids At day 28 | - | No association of UGT1A9 c.-331T>C variant with MPA pharmacokinetics | [43] |
|       | rs10176426 (-665C>T) | c.-665C: 4%-440/-331T/C: 41% c.-275A: 5% c.98C: 0% | Mixed | 338 adult patients (Belgium) | MMF Tacrolimus Corticosteroids One-year follow-up | UGT1A9 c.-2152CT and c.-275TA genotypes were associated with lower MPA AUC<sub>0-12</sub> on tacrolimus treatment, especially at day 3. c.98TC genotype was associated with higher AUC<sub>0-12</sub> | UGT1A9 c.-331C allele was associated with adverse events (especially leukopenia) | [39] |
|       | rs2741045 (c.-440C>T) | c.-2152T: 9% c.-331C: 28% c.-275A: 11% c.98C: 0% | Prospective, multicenter (FDCC Study) | 338 adult patients | MMF Tacrolimus Corticosteroids One-year follow-up | - | UGT1A9 c.-2152CT and c.-275TA genotypes were associated with lower MPA AUC<sub>0-12</sub> on tacrolimus treatment, especially at day 3. c.98TC genotype was associated with higher AUC<sub>0-12</sub> | UGT1A9 c.-331C allele was associated with adverse events (especially leukopenia) | [43] |
|       | rs2741046 (c.-331T>C) | c.-2152T: 9% c.-331C: 28% c.-275A: 11% c.98C: 0% | Prospective, multicenter (FDCC Study) | 338 adult patients | MMF Tacrolimus Corticosteroids One-year follow-up | - | UGT1A9 c.-2152CT and c.-275TA genotypes were associated with lower MPA AUC<sub>0-12</sub> on tacrolimus treatment, especially at day 3. c.98TC genotype was associated with higher AUC<sub>0-12</sub> | UGT1A9 c.-331C allele was associated with adverse events (especially leukopenia) | [43] |
|       | rs6714486 (c.-275T>A) | c.-2152T: 1% c.-1887G: 13% -665T: 4% -440/-331T/C: 41% c.-275A: 5% c.98C: 0% | Prospective | 100 adult patients (Japan) | MMF Tacrolimus Corticosteroids At day 28 | - | - | - |
|       | rs3832043 (-118delT) | c.-2152T: 1% c.-1887G: 13% -665T: 4% -440/-331T/C: 41% c.-275A: 5% c.98C: 0% | Prospective | 33 pediatric patients (USA) | MMF Tacrolimus Corticosteroids One-year follow-up | - | - | - |
|       | rs72551330 (UGT1A9*3, c.98T>C) | c.-2152T: 9% c.-331C: 28% c.-275A: 11% c.98C: 0% | Prospective | 80 adult patients (Japan) | MMF Tacrolimus Corticosteroids At day 28 | - | No association of UGT1A9 c.-331T>C variant with MPA pharmacokinetics | [45] |
|       | rs2741049 (I399T>C) | c.-2152T: 9% c.-331C: 28% c.-275A: 11% c.98C: 0% | Prospective | 100 adult patients (Belgium) | MMF Tacrolimus Corticosteroids Five-year follow-up | - | No association of UGT1A9 c.-2152C>T variant with low MPA exposure (AUC<sub>0-12</sub> < 30 mg/L h<sup>-1</sup>). | - |
|       | rs2741046 (c.-331T>C) | c.-2152T: 9% c.-331C: 28% c.-275A: 11% c.98C: 0% | Prospective | 133 adult patients - for PK profile n = 30 (Spain) | MMF Tacrolimus Corticosteroids One-year follow-up | UGT1A9 c.-2152C>T allele was associated with lower MPA exposure (AUC<sub>0-12</sub> or AUC<sub>6-12</sub>) | UGT1A9 c.-2152C>T 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 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 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 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 Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up | - | No association of *UGT1A9* c.-2152T>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 Tacrolimus 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 Tacrolimus Corticosteroids Six-month follow-up | - | No association of *UGT1A9* c.-2152C>T and c.-275T>A variants with AR or adverse events | [29] |
| c.-1818T: 13% c.-440T: 2% c.-331C: 2% -1818delT: 58% I399C: 31% | Prospective | 127 adult patients (China) | MMF Tacrolimus Corticosteroids | No association of *UGT1A9* c.-440CT (or c.-331TC) and -1818CC genotypes were associated with higher and lower MPAG AUC0-12, respectively | - | [35] |
| | Retrospective (Case-control) multicenter | 284 pediatric and young adult patients (USA) | MMF 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. |
|----------|------------------------|------------------|--------------------|--------------------------|----------------------------|-------------------|------------------------------------------------------------|------|
|          |                        |                  |                    |                           |                            | No association of UGT1A9 -118delT variant with MPA pharmacokinetics | [50] |
|          |                        |                  |                    |                           |                            | -                | No association of UGT1A9 c.-275T>A variant with AR          | [22] |
|          | c.-275A: 14%           |                  |                    |                           |                            | No association of UGT1A9 c.-275T>A and c.98T>C variants with MPA exposure (AUC) | [49] |
|          | c.98C: 0%              |                  |                    |                           |                            | No association of UGT1A9 c.-275T>A and C variants with neutrophil counts | [38] |
|          | c.-440T: 3%            |                  |                    |                           |                            | -                | UGT1A9 rs6744284CC genotype was associated with higher gastrointestinal symptom rating scale (GSRS) score for constipation at week 1 | [41] |
|          | c.-331C: 3%            |                  |                    |                           |                            | -                | -                                                          |      |
|          | c.1399C: 47%           |                  |                    |                           |                            | -                | -                                                          |      |
|          | rs6744284              | rs6744284T: 32%  |                    |                           |                            | No association of UGT1A9 c.-440C>T, c.-331T>C and I399 T>C variants with MPA C/D (days 3-8) | [53] |
|          |                        |                  |                    |                           |                            | -                | -                                                          |      |
| UGT2B7   | rs7438135              | c.-842G: 55%     | Prospective, multicenter | 92 adult patients (France) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | UGT2B7 c.-842AA (802CC) genotype was associated with higher AcMPAG AUC0-9 at Month 1 and 3, on sirolimus treatment (n = 40) | [53] |
|          | (c.-840G>A, c.-842G>A or c.-900G>A) |                       |                    |                           |                            | -                | -                                                          |      |
|          | rs7662029              | (c.-327G>A)      |                    |                           |                            | -                | -                                                          |      |
|          | rs73823859             | (c.-79G>A)       |                    |                           |                            | -                | -                                                          |      |
|          | rs12233719             | (c.211G>T)       |                    |                           |                            | -                | -                                                          |      |
|          | rs7439366              | UGT2B7*2(T): 33% | Prospective        | 72 adult patients (Japan) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | UGT2B7*2 variants showed higher MPA peak concentration than those with 802CC genotype | [36] |
|          | (802C>T, UGT2B7*2)    |                  |                    |                           |                            | -                | -                                                          |      |
|          | rs62988861             | (IVS1+985A>G)    | Prospective (FDCC Study) | 332 adult patients        | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | No association of UGT2B7 c.-840G>A variant with exposure to AcMPAG (level and AUCs) | [54] |
|          | c.-840G: 50%           | c.211G>T        |                    |                           |                            | -                | No association of UGT2B7 c.-900A>G variant with adverse events (diarrhea and leukopenia) | [43] |
|          | rs7439366              | UGT2B7*2(T): 33% | Prospective        | 72 adult patients (Japan) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | UGT2B7*2 variants showed higher MPA peak concentration than those with 802CC genotype | [36] |
|          | (802C>T, UGT2B7*2)    |                  |                    |                           |                            | -                | -                                                          |      |
|          | rs62988861             | (IVS1+985A>G)    | Prospective (FDCC Study) | 332 adult patients        | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | No association of UGT2B7 c.-840G>A variant with exposure to AcMPAG (level and AUCs) | [54] |
|          | c.-900G: 45%           | c.211G>T        |                    |                           |                            | -                | 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 |
|--------------|------------------|--------------|------------|----------------------------|------------------|-------------------|
| 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<sub>0-12</sub>) | 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 | UGT2B7 802T allele was associated with higher MPA apparent oral clearance | 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 IVS1+985AG genotype was associated with higher MPA AUC<sub>0-12</sub> | No association of UGT2B7 802C>T variant with AR or adverse events | [40] |
| c.-840G: 47% | Retrospective (Transgene study) | 218 adult patients (France) | MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up | UGT2B7 c.-900G allele was associated with increased risk of anemia. No association with AR, diarrhea, or leukopenia | No association of UGT2B7 c.-840G>A variant with gastrointestinal adverse events | [13] |
| c.-900G: 29% IVS1+985G: 5% c.211T: 14% | Prospective (Case-control) multicenter | 284 pediatric and young adult patients (USA) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up | UGT2B7 c.211G>T variant was associated with MPA initial volume of distribution and c.211GT genotype was associated with higher MPA exposure | In patients treated non-depleting antibodies, UGT2B7 c.-900G allele was associated with increased risk of leukopenia | [27] |
| c.-842G: 37% | Prospective (Case-control) | 145 adult patients (Brazil) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | UGT2B7 c.-842G allele was associated with prevention of AR | No association of UGT2B7 c.-842G>A, -79G>A and 802C>T variants with AR exposure (AUC<sub>0-12</sub>) | [22] |
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) | 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 | No association of ABCB1 c.3435T allele with higher requirement of MPA dose reduction due to diarrhea. No association of ABCB1 c.3435C>T variant with AR | [23] |
|      | rs3842 (417A>G) | c.1236T: 40% | Prospective, multicenter (CAESAR study) | 237 adult patients | MMF Tacrolimus 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] |
|      | rs1128603 (c.1236C>T) | c.2677G: 58% | Retrospective | 207 pediatric patients (Poland) | MMF or Azathioprine Tacrolimus Corticosteroids | - | No association of ABCB1 c.3435C>T variant with AR or AR-related toxicity | [26] |
|      | rs2032582 (c.2677G>T/A) | c.3435T: 55% | Retrospective | 218 adult patients (France) | MMF Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up | - | No association of ABCB1 c.3435C>T variant with AR or adverse events | [13] |
|      | rs1045642 (c.3435C>T) | c.3435T: 41% | Retrospective (Transgene study) | 408 adult patients (China) | MMF Tacrolimus Corticosteroids 40-day follow-up | No association of UGT2B7 c.211G>T and 802C>T variants with MPA exposure (AUC) | UGT2B7 rs7662209 GG genotype was possibly associated with higher MPA C/D (days 3-8) | [38] |

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: entericoated mycophenolate sodium salt; eGFR: estimated glomerular filtration rate; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MPAG: MPA-7-O-glucuronide
| Gene | Variant | Allele frequency | Study design | Population | Immunosuppressive regimen | Pharmacokinetics | Clinical outcomes | Ref. |
|------|---------|-----------------|--------------|------------|----------------------------|-----------------|-------------------|-----|
| ABCC2 | rs1885301 | -1549A: 38% -1023A: 13% -1019G: 43% | Prospective | 95 adult patients (Belgium) | MMF Tacrolimus Corticosteroids One-year follow-up | No association of ABCC1 c.1236C>T and c.2677G>T/A variants with exposure to MPA, MPAG or AcMPAG | No association of ABCC1 c.1236C>T, c.2677G>T/A and c.3435C>T variants with diarrhea or leukopenia | [59] |
| ABCC2 | rs7910642 | c.-24T: 23% c.1249A: 17% c.3972T: 32% c.4544A: 9% | Prospective | 97 adult patients (Brazil) | EC-MPS Tacrolimus Corticosteroids One-year follow-up | No association of ABCC2 c.-24C>T and c.3972C>T variants with AR or hematological disorders | No association of ABCC2 c.-24C>T variant with AR or hematological disorders | [24] |
| ABCC2 | rs2804402 | 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 | No association of ABCC2 c.-24C>T variant with diarrhea | [48] |
| ABCC2 | rs113646094 | 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] |
| ABCC2 | rs17222723 | c.3972T: 36% rs2804402G: 42% rs17222723A: 7% | Prospective, multicenter (CAESAR study) | 237 adult patients | MMF Cyclosporine 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 AR | [25] |
| ABCC2 | rs3740066 | c.4544G: 9% | Prospective | 100 adult patients (Belgium) | MMF Tacrolimus Corticosteroids Five-year follow-up | No association of ABCC2 c.-24C>T variant with MPA exposure | No association of ABCC2 c.-24C>T and c.3972C>T variants with MPA exposure (AUC<0.1) | [45] |
| ABCC2 | rs3740066 | c.4544G: 9% | Prospective | 100 adult patients (Belgium) | MMF Tacrolimus Corticosteroids Five-year follow-up | No association of ABCC2 c.-24C>T variant with MPA exposure | No association of ABCC2 c.-24C>T and c.3972C>T variants with MPA exposure (AUC<0.1) | [39] |

**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 Tacrolimus Corticosteroids One-year follow-up No association of ABC1 c.1236C>T, c.2677G>T/A and c.3435C>T variants with exposure to MPA, MPAG or AcMPAG No association of ABC1 c.1236C>T, c.2677G>T/A and c.3435C>T variants with diarrhea or leukopenia [59]

c.1236T: 36% c.2677T/A: 32/4% Prospective 97 adult patients (Brazil) EC-MPS Tacrolimus Corticosteroids One-year follow-up No association of ABC1 c.1236C>T and c.2677G>T/A variants with MPA C/D No association of ABC1 c.1236C>T and c.2677G>T/A variants with DGF or AR [24]

c.1236T: 36% c.3435T: 50% Retrospective (Case-Control), multicenter 284 pediatric and young adult patients (USA) MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids One-year follow-up - No association of ABC1 c.1236C>T, c.2677G>T/A and c.3435C>T variants with diarrhea or 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 ABC1 c.1236C>T and c.2677G>T/A variants with MPA C/D No association of ABC1 c.1236C>T and c.2677G>T/A variants with DGF or AR [24]

c.1236T: 36% c.3435T: 50% Prospective 97 adult patients (Brazil) EC-MPS Tacrolimus Corticosteroids One-year follow-up No association of ABC1 c.1236C>T and c.2677G>T/A variants with MPA C/D No association of ABC1 c.1236C>T and c.2677G>T/A variants with DGF or AR [24]

c.1236T: 36% c.3435T: 50% Prospective 97 adult patients (Brazil) EC-MPS Tacrolimus Corticosteroids One-year follow-up No association of ABC1 c.1236C>T and c.2677G>T/A variants with MPA C/D No association of ABC1 c.1236C>T and c.2677G>T/A variants with DGF or AR [24]

c.1236T: 36% c.3435T: 50% Prospective 97 adult patients (Brazil) EC-MPS Tacrolimus Corticosteroids One-year follow-up No association of ABC1 c.1236C>T and c.2677G>T/A variants with MPA C/D No association of ABC1 c.1236C>T and c.2677G>T/A variants with DGF or AR [24]
| 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 | 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 | 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 (Transgene study) | 89 pediatric patients (France) | MMF Cyclosporine Tacrolimus Sirolimus Corticosteroids | No association of ABCC2 c.-24C>T, c.1249G>A, 3563T>A and c.3972C>T variants with MPA pharmacokinetics | -                                                    | [40] |
| c.-24T: 19% 1446G: 0.7% c.3972T: 35% |         |                 | Retrospective (Transgene study) | 218 adult patients (France) | MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids | No association of ABCC2 c.-24C>T and c.1249G>A, 1446G>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 | ABC2 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 | 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 | 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 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 Corticosteroids | | | - | 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, 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 Sirolimus Corticosteroids | 40-day follow-up | | No association of ABCC2 c. -24C>T, c.1249G>A variants with MPA exposure (AUC) | - | [38] |
| ABCG2 | rs2231142 (c.421C>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] |
| | rs4491984G>A | c.421A: 8% | Prospective, multicenter (Brazil) | 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. |
|-------------------------------|-------------|------------|---------------------------|------------------|------------------|-----|
| ABGG2 c.421A: 10%            | Prospective | 97 adult patients (Brazil) | EC-MPS Tacrolimus Corticosteroids One-year follow-up | No association of *ABGG2* c.421A variant with MPA C/D | No association of *ABGG2* c.421A variant with DGF or AR | [24] |
| rs4491984 A: 50%             | Retrospective | 408 adult patients (China) | MMF Tacrolimus Corticosteroids 40-day follow-up | No association of *ABGG2* c.421A and rs4491984 variants with MPA C/D (days 3-8) | - | [38] |
| SLCO1B1 c.421A: 31% rs4491984 A: 50% | Prospective | 87 adult patients (Japan) | MMF Tacrolimus Corticosteroids At day 28 | No association of *SLCO1B1* c.1A, c.1B and c.15 variants with MPA pharmacokinetics | - | [65] |
| rs4149015 (-11187G>A)         | Prospective | 218 adult patients (France) | MMF Tacrolimus Corticosteroids At point between 3-6 months | No association of *SLCO1B1* c.388A>G, 463C>A and c.521T>C variants with MPA or MPAG pharmacokinetics | - | [13] |
| rs2306283 (c.388A>G)         | Prospective (Transgene study) | 185 patients (France) | MMF Tacrolimus Corticosteroids One-year follow-up | No association of *SLCO1B1* c.388A>G, 463C>A and c.521T>C variants with MPA or MPAG pharmacokinetics | - | [14] |
| rs11045819 (463C>A)          | Prospective (included multicenter Apomygre study) | 338 adult patients (France) | MMF 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] |
| rs4149056 (c.521T>C or Val174Ala) | Prospective (FDCC Study) | 284 pediatric and young adult patients (USA) | MMF Tacrolimus Corticosteroids One-year follow-up | - | No association of *SLCO1B1* rs4149056 and rs11045819 variants with leukopenia | [27] |
| rs11045819 (Pro155Thr)       | Prospective | 284 adult patients (Brazil) | MMF Tacrolimus Corticosteroids One-year follow-up | - | No association of *SLCO1B1* c.521T>C variant with AR | [22] |
| SLCO1B1 rs4149056 c.521T>C   | Prospective | 145 adult patients (Brazil) | MMF Tacrolimus Corticosteroids One-year follow-up | - | 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. |
|--------------|-----------------|--------------|------------|----------------------------|------------------|------------------|------|
| SLC10A1 | c.388G: 48% 463A: 10% | Prospective | 21 adult patients (Canada) | MMF Tacrolimus Corticosteroid-free One-year follow-up | No association of SLC10A1 c.388A>G and 463C>A variants with MPA exposure (AUC) | No association of SLC10A1 c.388A>G and 463C>A variants with neutrophil counts | [49] |
| SLC10A3 | rs4149117 (c.334T>G) 699G: 34% | Prospective | 87 adult patients (Japan) | MMF Tacrolimus Corticosteroids At day 28 | No association of SLC10A3 c.334T>G (or 699G>A) variant with diarrhea | - | [65] |
| rs7311358 (c.699G>A) | | | | | | | |
| rs1104585 | | Retrospective (Transgene study) | 218 adult patients (France) | MMF Cyclosporine Tacrolimus mTOR inhibitor Corticosteroids One-year follow-up | - | No association of SLC10A3 c.334T>G variant with AR or adverse events | [13] |
| rs60140950 (c.767G>C) | c.334T: 17% | | | | | | |
| 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 | No association of SLC10A3 c.334G>A variant with lower MPA peak concentration and exposure (AUC<sub>4-12</sub>) 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 SLC10A3 c.334T>G (or 699G>A) variant with exposure to MPA, MPAG or AcMPAG | No association of SLC10A3 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 SLC10A3 c.334T>G variant with MPA or MPAG exposure (AUC<sub>4-12</sub> or AUC<sub>0-12</sub>) | - | [37] |
| c.334T: 15% | Prospective, multicenter (Dominos study) | 189 adult patients (France) | EC-MPS Cyclosporine Corticosteroids Six-month follow-up | - | No association of SLC10A3 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 SLC10A3 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 SLC10A3 c.334T>G variant with MPA C/D (days 3-8) | - | [38] |
confirmed by Varnell et al.\cite{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\cite{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\cite{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\cite{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\cite{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\cite{32}. UGT1A7, UGT1A8 and UGT1A10 are absent in the liver but are expressed in other tissues, such as the intestine. 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\cite{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.\cite{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) without detectable changes in MPA exposure (AUC) 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 AUC0-12 in cyclosporine-treated patients from the FDCC Study [39], and lower MPAG AUC0-12 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.518G 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 [8,32].

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 (AUC0-12 used as marker) in kidney patients on MPA and tacrolimus treatment [19,45,46]. Kuypers et al. [67] also reported this finding but only among patients treated with 2 g MMF, and van Schaik et al. [68] 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\textsuperscript{[14,40,48,49]}. 

\textit{UGT1A9} rs2741046 (c.-331T>C), in complete linkage with rs2741045 (c.-440C>T)\textsuperscript{[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, \textit{UGT1A9} c.-440 TT and -665CT genotypes were associated with higher MPA exposure (AUC\textsubscript{0-2}, AUC\textsubscript{0-4}, AUC\textsubscript{0-12} or C/D), but not with MPAG AUC\textsubscript{0-12}\textsuperscript{[48]}. On the contrary, \textit{UGT1A9} c.-440CT and -1818CC genotypes were associated with higher and lower MPAG AUC\textsubscript{0-12}, respectively, in Chinese patients on tacrolimus treatment\textsuperscript{[35]}. Moreover, no association was found with MPA or MPAG pharmacokinetics in other studies\textsuperscript{[14,38]}. 

The variants \textit{UGT1A9} rs3832043 (-118delT), rs72551330 (c.98T>C) and rs2741049 (c.98T>C or IVS1 + 399T>C) do not seem to influence MPA or MPAG pharmacokinetics in kidney transplant patients\textsuperscript{[14,33,35,38,40,47,49,50]}. Nevertheless, higher MPA AUC\textsubscript{0-12} was associated with the presence of \textit{UGT1A9} c.98TC genotype in one study with 338 patients\textsuperscript{[39]}. Although this result is in accordance with the low activity related to \textit{UGT1A9} c.98T>C variant, the c.98C allele frequency was 2%\textsuperscript{[9,39]}. Furthermore, the low frequency of the \textit{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 \textit{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\textsuperscript{[13,22,27,29,34,47-49]}. In line with the aforementioned subtherapeutic levels of immunosuppression, \textit{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, \(P = 0.042\))\textsuperscript{[39]} in patients treated with MPA and tacrolimus. However, another investigation found that \textit{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\textsuperscript{[46]}. A greater severity of diarrhea and heartburn was also associated with these variants. Moreover, the \textit{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\textsuperscript{[41]}. 

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

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

\textbf{UGT2B7}

\textbf{UGT2B7} is the key enzyme involved in \textit{AcMPAG} formation. Djebli \textit{et al}.\textsuperscript{[53]} investigated the \textit{in vivo} and \textit{in vitro} effect of \textit{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 \textit{AcMPAG} production was higher in the presence of \textit{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), \textit{UGT2B7} c.-900AA (or 802CC) genotype was associated with higher \textit{AcMPAG} AUC\textsubscript{0-9} at month 1 and 3 after transplantation\textsuperscript{[52]}. Likewise, no association with exposure to \textit{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 \textit{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 transcripational activity of the reporter gene in Caco-2 and HepG2 cells, was not associated with MPA exposure\(^{[38,56]}\). 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 \textit{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, \(P = 0.003\))\(^{[28]}\). 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 \textit{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\(^{[55]}\).

Wang \textit{et al.}\(^{[14]}\) 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 \([1]\). 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 \([1]\), 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.-24T allele 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\text{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\cite{14,24,37,39,45,48,49,65,66}.

Regarding clinical outcomes, Naesens et al.\cite{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\cite{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\cite{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 c.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\cite{24,27,36,37,38}.

SLCO1B1, SLCO1B3 and SLCO2B1

OATPs additionally contribute to drug disposition, with ABC proteins; however, OATPs do not depend directly on using cellular ATP\cite{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\cite{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)\cite{14}. In line with this, Michelon et al.\cite{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)\cite{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\cite{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\cite{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\cite{13}. Possibly
because cyclosporine inhibits OATP1B1, the effect of the SLCO1B1 c.521C allele was not detectable in the therapy with this immunosuppressant\cite{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)\cite{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\cite{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\cite{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\cite{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\cite{14}, or tacrolimus\cite{37,38,59}. On the contrary, the SLCO1B3 c.334GG (699AA) genotype was associated with higher MPA AUC6-12, considered a marker of MPA recirculation, in Japanese patients with tacrolimus-based therapy at day 28 after transplantation\cite{65}.

SLCO1B3 c.334T>G (or 699G>A) and rs1104585 variants were not associated with AR, leukopenia, diarrhea or other adverse events\cite{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\cite{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\cite{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\cite{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 rs2278293 and rs2278294 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 C0 ≥ 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\[23\]. 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\[71\], Apomygree and FDCC studies\[23\], 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     | rs228075 C>T  | c.1320A: 22%     | Prospective, multicenter      | 237 adult patients | MMF                        | No association of IMPDH1 rs228075 variant with AR                                  | [25]       |
|            | rs227893 C>T  | c.579+119G>A     | Prospective, multicenter      | 456 adult patients | MMF                        | IMPDH1 rs227893 A allele was associated with reduced risk of AR and increased risk of leukopenia No association of rs227893 with AR, leukopenia, CMV and other infections | [72]       |
|            | rs2278294 C>T | c.580-106G>A     | Prospective                   | 82 adult patients (Japan) | MMF                        | IMPDH1 rs2278294 A allele was associated with reduced risk of AR and increased risk of leukopenia No association of rs2278294 with AR, leukopenia, CMV and other infections | [74]       |
| rs2278293 A: 46% |        | Prospective, multicenter (Apomygre and FDCC studies) | 456 adult patients | MMF                        | IMPDH1 rs2278294 A allele was associated with reduced risk of AR and increased risk of leukopenia No association of rs227893 with AR, leukopenia, CMV and other infections | [72]       |
|           | rs2278294 A: 45% |        | Prospective                   | 82 adult patients (Japan) | MMF                        | IMPDH1 rs2278294 A allele was associated with reduced risk of AR and increased risk of leukopenia No association of rs227893 with AR, leukopenia, CMV and other infections | [74]       |
|           |                          | Retrospective (Transgene study) | 218 adult patients (France) | MMF                        | No association of IMPDH1 variants with MPA-related AR or leukopenia               | [13]       |
| rs228075 T: 25% | rs2278923 T: 47% | Retrospective | 191 adult patients (USA) | MMF                        | The variants IMPDH1 rs228075 and rs2278923 were associated with reduced risk of AR No association of IMPDH1 variants with leukopenia 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) | [71]       |
| rs2278923 A: 43% | rs2278294 A: 40% | Retrospective, multicenter (Collaborative Transplant study) | 1,040 adult patients | MMF                        | 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]       |
| rs2278294 A: 40% |                          | Retrospective, 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: - | Retrospective (Case-control), multicenter | 284 pediatric and young adult patients (USA) | MMF                        | 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% and A: 45%| Retrospective    | 145 adult patients (Brazil)   | MMF, Cyclosporine, Tacrolimus, Sirolimus, Corticosteroids | One-year follow-up                               | No association of IMPDH1 variant with AR                                        | [22] |
|            | A: 30%           | Case-control     |                               |                              |                                                    |                                                                                  |      |
| rs2278294  | A: 45%           | Prospective      | 190 adult patients (Brazil)   | MMF, Cyclosporine, Tacrolimus, Sirolimus, Corticosteroids | One-year follow-up                               | IMPDH1 rs2278294 G allele was associated with slower BMI gain                   | [75] |
| IMPDH2     | rs11706052 A>G   | Prospective, multicenter | 237 adult patients | MMF, Cyclosporine, Tacrolimus, Sirolimus, Corticosteroids | Five-year follow-up                               | IMPDH2 rs11706052 G allele was associated with increased risk of AR             | [25] |
|            | (c.819+10T>C, also known as 3757T>C) | (CAESAR study) |                              |                              |                                                    |                                                                                  |      |
| rs121434586| T: 0.3%          | Retrospective    | 191 adult patients (US)       | MMF, Cyclosporine, Tacrolimus, Sirolimus, Prednisone | One-year follow-up                               | No association of IMPDH2 variant with AR or leukopenia                         | [71] |
| rs4974081  | (-3624A>G)       | Prospective      | 101 adult patients (Netherlands) | MMF, Tacrolimus, Sirolimus, 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) | [78] |
| IMPDH2     | rs11706052 C: 9% | Prospective (Apomygre and FDCC studies) | 456 adult patients | MMF, Cyclosporine, Tacrolimus, Sirolimus, Prednisone | 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) | [72] |
| rs4974081  | G: 24%           | Prospective      | 177 adult patients (Poland)   | MMF, Calcinurin inhibitors, 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) | [80] |
| rs11706052 | G: 19%           | Prospective, multicenter | 1,040 adult patients | MMF, Cyclosporine, Tacrolimus, Sirolimus, Prednisone | 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) | [73] |
|             | (Collaborative Transplant study) | (Dominos study) |                              |                              |                                                    |                                                                                  |      |
| rs11706052 | C: 11%           | Prospective, multicenter | 189 adult patients | EC-MPS, Cyclosporine, Tacrolimus, Corticosteroids | Six-month 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) | [29] |

| Gene       | Variant          | Allele frequency | Study design                  | Population                   | Immunosuppressive regimen                          | Clinical outcomes                                                                 | Ref. |
|------------|------------------|------------------|-------------------------------|------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------|------|
| rs2278293  | A: 47% and A: 45%| Retrospective    | 145 adult patients (Brazil)   | MMF, Cyclosporine, Tacrolimus, Sirolimus, Corticosteroids | One-year follow-up                               | No association of IMPDH1 variant with AR                                        | [22] |
|            | A: 30%           | Case-control     |                               |                              |                                                    |                                                                                  |      |
| rs2278294  | A: 45%           | Prospective      | 190 adult patients (Brazil)   | MMF, Cyclosporine, Tacrolimus, Sirolimus, Corticosteroids | One-year follow-up                               | IMPDH1 rs2278294 G allele was associated with slower BMI gain                   | [75] |
| IMPDH2     | rs11706052 A>G   | Prospective, multicenter | 237 adult patients | MMF, Cyclosporine, Tacrolimus, Sirolimus, Prednisone | Five-year follow-up                               | IMPDH2 rs11706052 G allele was associated with increased risk of AR             | [25] |
|            | (c.819+10T>C, also known as 3757T>C) | (CAESAR study) |                              |                              |                                                    |                                                                                  |      |
| rs121434586| T: 0.3%          | Retrospective    | 191 adult patients (US)       | MMF, Cyclosporine, Tacrolimus, Prednisone | One-year follow-up                               | No association of IMPDH2 variant with AR or leukopenia                         | [71] |
| rs4974081  | (-3624A>G)       | 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) | [78] |
| IMPDH2     | rs11706052 C: 9% | Prospective (Apomygre and FDCC studies) | 456 adult patients | MMF, Cyclosporine, Tacrolimus, Prednisone | 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) | [72] |
| rs4974081  | G: 24%           | Prospective      | 177 adult patients (Poland)   | MMF, Calcinurin inhibitors, 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) | [80] |
| rs11706052 | G: 19%           | Prospective, multicenter | 1,040 adult patients | MMF, Cyclosporine, Tacrolimus, Prednisone | 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) | [73] |
|             | (Collaborative Transplant study) | (Dominos study) |                              |                              |                                                    |                                                                                  |      |
| rs11706052 | C: 11%           | Prospective, multicenter | 189 adult patients | EC-MPS, Cyclosporine, Tacrolimus, Corticosteroids | Six-month 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) | [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 Tacrolimus Cyclosporine 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 Tacrolimus Cyclosporine Sirolimus 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: mycophenolic acid

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. Eight other variants in IMPDH1 were also identified by Wang et al., but no association with leukopenia was found.

Woillard et al. 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.

Pazik et al. 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. 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. 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.
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[35]. 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[72] 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 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[75] 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[15,72,73,76-80], ABCB1 rs2032582[10], ABCC2 rs2273697[64,65], and rs717620[66], CYP2C8 rs11572070[28], UGT1A8 rs1042559[34], UGT1A9 rs3832043[80,84], rs6714486[84,47,51], rs17868320[47,51], and rs72551330[51], UGT2B7 rs7438135[28], SLC01B1 rs4149056[13,59] and rs2306283[83], and SLC01B3 rs7311358[13,65] and rs4149117[13,14,59,65]. All these variants are assigned as evidence level 3 with exception of SLC01B3 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 AUC₀-₁₂ 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[88,90]. 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

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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

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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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