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# Systematic Review of Pharmacogenetics of Immunosuppressants in Heart Transplantation

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**Abstract:** The standard immunosuppressive treatments in heart transplantation are calcineurin inhibitors, corticosteroids, and antimetabolite agents or inhibitors of the mammalian target of rapamycin. Pharmacogenetic studies show the impact on clinical course of genetic variability in genes that encode transporters, metabolizers, or molecular targets of immunosuppressants. The aim of this systematic review is to elucidate the role that pharmacogenetics of immunosuppressant drugs plays in clinical outcomes upon heart transplantation. PubMed, EMBASE, the Cochrane Central Register, and the Database of Abstracts of Reviews of Effects were searched without restrictions. The 64 studies analyzed followed these criteria: (1) were based on clinical data on heart transplantation patients; (2) analyzed the associations between polymorphisms and clinical response; (3) analyzed the impact of polymorphisms on immunosuppressant safety. CYP3A4/5 variants were associated with higher doses of tacrolimus, whereas POR*28 variants with lower doses—ABCB1, ABCC2, SLCO1B1, and SLC13A1—contribute to interindividual variability in drug absorption, distribution, and toxicity. An ABCC2 polymorphism (rs717620) was related to higher risk of graft rejection in pediatrics. Variations in HLA-G, TNF-$\alpha$ and TGF-$\beta$ genes influence transplant rejection risk and immune response. Implementing pharmacogenetic screening of polymorphisms could enhance therapeutic outcomes by improving drug efficacy, reducing toxicity, and ultimately increasing heart graft survival rates. Strong evidence supports genotyping for CYP3A5 and TPMT, but further research is required for transporter genes and cytokine polymorphisms.

**Keywords:** tacrolimus; cyclosporine; mycophenolic acid; cardiac transplant; precision medicine; CYP3A5

## 1. Introduction

Standard immunosuppressive therapy in heart transplantation consists of a calcineurin inhibitor (CNI), typically tacrolimus in most cases or alternatively cyclosporine; an antimetabolite agent as complementary treatment, mainly mycophenolate mofetil (MMF) or azathioprine; and corticosteroids [1]. In certain situations, inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus and everolimus, are used as a substitute for MMF. Both CNIs have a narrow therapeutic window, making pharmacokinetic monitoring essential to maintain adequate serum levels that maximize therapeutic efficacy while minimizing toxicity.

The variability observed in heart transplantation outcomes cannot be fully explained by clinical factors alone. Pharmacogenomics offers a pathway to personalized medicine by integrating patient-specific data, clinical parameters, and genetic profiles. Research in pharmacogenetics highlights how genetic differences in transporter proteins, metabolic enzymes, and molecular targets of immunosuppressive drugs can significantly influence therapeutic responses.

The aim of this systematic review is to elucidate the role that pharmacogenetics of immunosuppressant drugs plays in clinical outcomes upon heart transplantation, including tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, sirolimus, everolimus, and corticosteroids. There is established evidence of the impact that polymorphisms in certain candidate genes have on immunosuppressive therapy [2]. For instance, variations in CYP3A5 significantly influence the pharmacokinetics of tacrolimus, which is crucial for determining the appropriate initial dose. Polymorphisms in ABCB1 have been linked to graft rejection and nephrotoxicity associated with calcineurin inhibitors, while TPMT variants affect the clearance and toxicity of azathioprine. Additionally, other genes involved in immunosuppressive pathways are being investigated for their potential clinical relevance, in which their influence remains unclear. As such, they will be studied in this review.

## 2. Materials and Methods

Following the PRISMA guidelines, a systematic search was independently conducted by three reviewers (TPP, MFS, and JEMV). The databases searched without restrictions included PubMed, EMBASE, the Cochrane Central Register, and the Database of Abstracts of Reviews of Effects (DARE). Additionally, reference lists from key studies and reviews were manually screened. The final literature search was completed on 29 May 2023.

Consistent search terms were applied across databases: (Tacrolimus [Mesh] OR Cyclosporine [Mesh] OR Everolimus [Mesh] OR Mycophenolic Acid [Mesh] OR Sirolimus [Mesh]) and Heart Transplantation [Mesh] and (Genetic Polymorphisms OR Single Nucleotide OR Pharmacogenetic* OR Polymorphism* OR SNP*).

A study selection was performed independently by two reviewers. In cases of disagreement, a third reviewer (JEMV) resolved the conflict. Studies were included if they met the following criteria: (1) based on clinical data from heart transplant recipients (excluding preclinical and in vitro studies); (2) examined associations between genetic polymorphisms and clinical response to immunosuppressants; (3) assessed the impact of polymorphisms on the safety profile of immunosuppressive therapies.

## 3. Results

Our systematic search yielded 119 citations from databases and journals, along with 12 additional records identified through other sources (Figure 1). Of the 82 citations selected for full-text review, 64 met the inclusion criteria and were ultimately included in the analysis (Figure 1). The level of agreement between reviewers during the study selection process was excellent, with a kappa coefficient of 0.96. The study analyzed the most relevant relationships between immunosuppressants and metabolizing enzymes, membrane transporters, and immunomodulatory pathways (Figure 2).

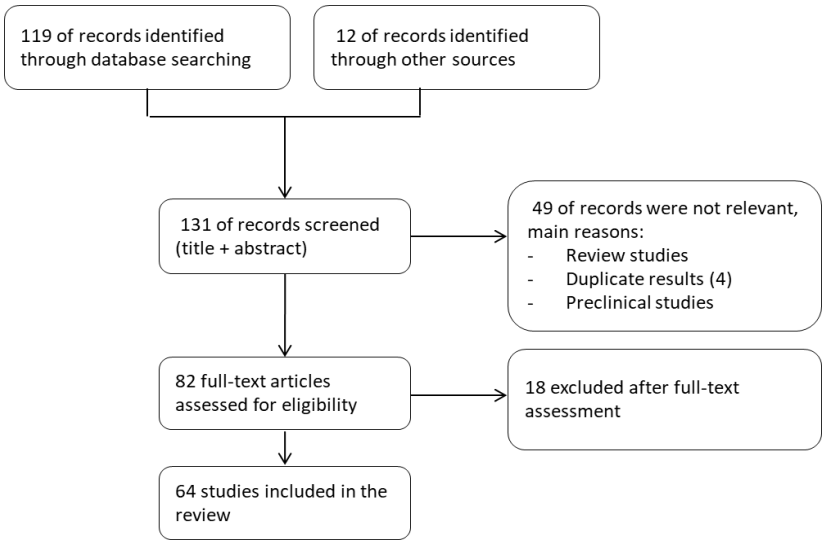


**Figure 1.** Review flowchart of evidence search and selection.

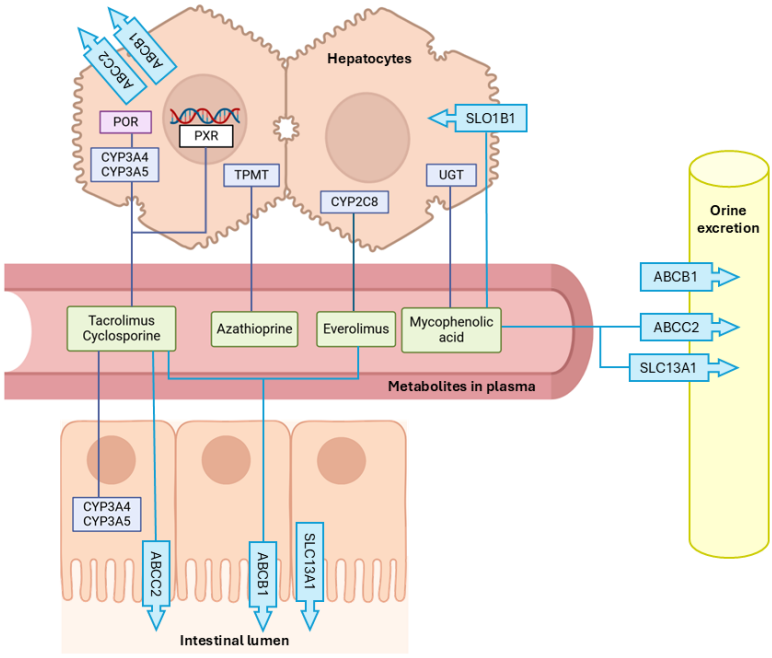


**Figure 2.** Most relevant relationships among immunosuppressants and enzymes and transporters included in the study. Abbreviations: ABCB1, ATP-binding cassette transporter B family member 1; ABCC2, ATP-binding cassette subfamily C member 2; POR, cytochrome P450 oxidoreductase; CYP, cytochrome P450; PXR, pregnane X receptor; TPMT, thiopurine methyltransferase; SLO1B1, solute carrier organic anion transporter family member 1B1; UGT, uridine glycosyltransferase; SLC13A1, solute carrier family 13 member 1.

### *3.1. Immunosuppressant Metabolizing Enzymes*

#### 3.1.1. Cytochrome P450 (CYP) and Other Related Genes

CNIs are inactivated by CYP3A in both the gastrointestinal system and the liver. While the primary isoform responsible for cyclosporine metabolism is CYP3A4, the most well-characterized variant and the predominant enzyme for tacrolimus metabolism is CYP3A5.

- CYP3A4

CYP3A4 is the primary enzyme of the cytochrome P450 superfamily responsible for the metabolism of numerous drugs. Its activity exhibits up to a 100-fold variation among individuals in the general population [3]. Tacrolimus, a cornerstone in the immunosuppressive treatment of heart transplantation, is extensively metabolized in the liver primarily through CYP3A4, with great interpatient variability (Table 1). Polymorphism CYP3A4*18B (rs2242480) results in increased enzymatic activity and this produces an increase in apparent oral clearance of the drug [4]. In a study involving 177 patients, individuals who lacked CYP3A5 expression and carried either the CYP3A4 1B (rs2740574) or 1G (rs2242480) alleles exhibited lower dose-adjusted trough concentrations of tacrolimus at two months, compared to those with the CYP3A4*1/*1 genotype [5]. In a pediatric study, carriers of the CYP3A4 22 allele required approximately 30% lower doses of tacrolimus to reach target blood concentrations compared to individuals with the CYP3A4*1/*1 genotype. Furthermore, early graft rejection occurred in three patients, all of whom were carriers of the CYP3A4*1/*1 genotype [6]. In another pediatric study with 66 patients, the initial concentration/dose ratio in patients with wild-type CYP3A4*1G (*1/*1) was approximately 1.7-fold higher than in those carrying at least one variant allele (*1/*G and *G/*G). Thus, patients carrying the CYP3A4 *1G mutation required 1.3-fold more than those with its wild-type variant [7].

Sirolimus and everolimus were also primarily metabolized in the liver by CYP3A4, and, to a lesser extent, by CYP3A5, but no relevant influence of genetic variability has been reported in heart transplantation, although published data is scarce.

- CYP3A5

The CYP3A5 enzyme constitutes at least 50% of the total hepatic CYP3A content in individuals who express it, making it a key genetic determinant of interindividual variability in the elimination of drugs metabolized by CYP3A5 [6] (Table 1). Both intestinal and hepatic CYP3A5 enzymes play a significant role in the first-pass metabolism of orally administered tacrolimus. Notably, CYP3A5 exhibits polymorphic expression, contributing to variability in drug bioavailability among individuals, with the genotype of SNP rs776746 being one of the most studied. The wild-type allele CYP3A5 1 is associated with high expression of functional CYP3A5 protein, whereas the variant allele CYP3A5 3 results in markedly reduced or absent enzyme expression [8]. Significant differences in tacrolimus, dose-normalized plasma concentrations have been observed between CYP3A5 expressers and non-expressers. Patients carrying the high-activity CYP3A5 variant required higher tacrolimus doses to achieve therapeutic levels compared to non-expressers [9]. In this regard, in a pediatric, the initial concentration/dose ratio of tacrolimus in CYP3A5 non-expressers (*3/*3) was found to be approximately twice as high as that observed in CYP3A5 expressers (*1/*1 and *1/*3), indicating significantly reduced metabolic activity in non-expressers [7]. The results are consistent when analyzing the combined genotype with CYP3A4 variants, with extensive metabolizers having greater requirements than intermediate and poor metabolizers [3]. The increase in plasma concentrations associated with poor metabolizing phenotypes has also been demonstrated in the case of cyclosporine [2]. In the case of everolimus, no differences were reported in concentration or dose between genotypes of expressing and

non-expressing variants [10]. The CYP3A5 genotype was related to the estimated glomerular filtration rate (eGFR) after transplantation, with a nephroprotective effect appearing in CYP3A5*1 allele carriers treated with cyclosporine or tacrolimus [11].

- CYP2C8

CYP2C8 is a drug-metabolizing enzyme that participates in the systemic clearance of everolimus (Table 1). In a cohort of 104 patients, the following polymorphisms were investigated: CYP2C8*1C (rs17110453), CYP2C8*1B (rs7909236), CYP2C8*3 (rs11572080 and rs10509681), and other variants (rs372775254, rs7912549, rs11572078, rs2275622, rs1934951). Different studies have found no significant association between CYP2C8 genotypes and either the dose requirements or plasma levels of everolimus. Furthermore, the analyzed CYP2C8 variants were not linked to the occurrence of adverse events [12]. In another study, 21 subjects carrying the CYP2C8*1/*1 genotype and 9 subjects carrying the CYP2C8*1/*3 genotype were analyzed and neither dose nor levels of everolimus were correlated with CYP2C8 genotype at any time point [12].

- Cytochrome P450 oxidoreductase (POR)

POR is a key modulator of cytochrome P450 enzyme activity. It is a microsomal flavoprotein that facilitates electron transfer from NADPH to CYP enzymes, enabling their catalytic function. The POR 28 variant (rs1057868), which results in an A503V amino acid substitution, has been associated with altered CYP enzyme activity, leading to significantly higher dose-adjusted tacrolimus concentrations indicating a lower dose requirement in patients, mainly in months 3 and 6 after transplantation [13]. Another POR polymorphism (rs2868177) has not found statistically significant differences in concentration/dose ratio and dose of immunosuppressants studied [14].

- Nuclear Receptor Subfamily 1 Group I Member 2 (NR1I2)/Pregnane X Receptor (PXR)

NR1I2, also known as PXR, has been shown to regulate the activity of CYP3A enzymes and may influence the pharmacokinetics of drugs metabolized by the cytochrome P450 system [15]. The PXR G25385T variant influenced tacrolimus dose requirement early (month 1) after heart transplantation [16]. However, another polymorphism (rs3814055) has not shown influence on the pharmacokinetics of immunosuppressants analyzed [14].

- Uridine glycosyltransferase (UGT)

Mycophenolic acid (MPA) is primarily metabolized by UGTs into two major metabolites: MPA glucuronide (MPAG) and acyl-MPA glucuronide (AcMPAG). There are several UGTs implied in MPA metabolism, and these enzymes are very polymorphic (Table 1). However, the influence of UGT polymorphisms on plasma MPA concentrations appears to be moderate and should be interpreted in conjunction with polymorphisms in ABCC2 and ABCB1. In a cohort of 68 thoracic transplant recipients—comprising 36 lung and 32 heart transplant patients—two variants of UGT2B7 (rs7439366 and rs73823859) were found to be associated with acyl-MPA glucuronide levels in both subgroups [17]. In this study, two UGT2B7 variants (rs7668258 and rs73823859) were significantly associated with thoracic graft rejection. Additionally, the UGT1A7 variant rs11692021 was linked to the occurrence of anemia, while the UGT 3′UTR T1813 variant was associated with leukopenia. However, in a Spanish cohort, the 3 SNPs of UGT1A9 studied were not related to MPA clearance and toxicities [15].

- Inosine monophosphate dehydrogenase (IMPDH)

De novo purine synthesis in activated lymphocytes is catalyzed by IMPDH. MPA reversibly inhibits IMPDH, causing decreased B- and T-cell proliferation and decreased antibody production. IMPDH isoform type II predominates in activated lymphocytes,

whereas isoform I predominates in mature lymphocytes. Surprisingly, the presence of polymorphisms in IMPDH1 and IMPDH2 genes does not consistently result in reduced enzymatic activity [18] (Table 1). In a cohort of 59 pediatric cardiac transplant recipients, two IMPDH1 variants (rs2278294 and rs2228075) were significantly associated with increased gastrointestinal toxicity [19]. Additionally, the G allele of the IMPDH2 rs11706052 polymorphism was linked to neutropenia, requiring temporary discontinuation of therapy. A subsequent haplotype analysis confirmed the association between IMPDH1 variants and gastrointestinal intolerance, although the haplotype effect was not stronger than that of the individual polymorphisms [20].

- Thiopurine methyltransferase (TPMT)

Azathioprine is used as an alternative antimetabolite in patients who are intolerant to mycophenolate formulations (MFF). As a prodrug, it is converted into 6-mercaptopurine within erythrocytes, with thiopurine S-methyltransferase (TPMT) serving as the primary enzyme responsible for its metabolism. Polymorphisms in the TPMT gene lead to reduced enzymatic activity, increasing the risk of adverse effects such as bone marrow suppression due to elevated levels of 6-thioguanine. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued guidelines for the clinical use of TPMT genotyping in patients treated with azathioprine, and the U.S. Food and Drug Administration (FDA) also recommends TPMT testing [21]. In heart transplant recipients, individuals heterozygous for TPMT variants (rs1142345, rs1800460, rs1800462) have shown reduced enzyme activity and experienced earlier and more frequent episodes of rejection compared to wild-type genotypes, although no significant differences in leukopenia incidence were observed [22].

**Table 1.** Characteristics of the studies included in systematic review of immunosuppressant metabolizing enzymes, including CYP and other genes [2-4,16-17,19,22-37].

| SNP | Study | n | Age Recipient (Range) | Age Donor (Range) | Ethnia Recipient | Ethnia Donor | HWE | Immunossu-presant Scheme | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| ***CYP3A4*** | | | | | | | | | |
| *CYP3A4*18B (C > T) rs2242480* | Cheng 2023 [4] | 53 | 48.45 ± 11.78 | NR | Unknown (China) | NR | Yes | TAC + MMF + CORT | • Variables affecting CL/F: albumin, POD, and gene rs2242480 (CYP3A4*18B): CL/F = [16.87 × (ALB/39.3) − 0.9565 × (POD/26)0.4460 × (1 + 0.3546 × (rs2242480 − TT)) × (1 + 0.5815 × (rs2242480 − CT))] × exp (CL) |
| *CYP3A4 (C > A,G,T) (rs2740574)* | Díaz-Molina 2012 [23] | 65 | 54.55 ± 10 | NR | Unknown (Spain) | NR | NR | TAC + MMF + PRED | ▪ CYP3A4 expression was not associated with TAC concentrations. ▪ CYP3A4 expression was not associated with the frequency of new-onset diabetes after transplantation. |
| *390 A > G (rs2740574)* | Isla 2009 [24] | 30 | 43 ± 14 | NR | Caucasian | NR | Yes | CSA ± AZA/MMF/CORT/ SIR ± BSX/ATG | ▪ CSA AUC(0–12h), Cmax, tmax, Css: no significant differences. |
| *390 A > G (rs2740574)* | Liu 2024 [5] | 177 | 54 | NR | Unknown (USA) | NR | NR | TAC | ▪ *1B reported as c-392G > A and rs2740574 and *1G as c1026 + 12G > A and rs2242480 but which variant is star allele is not completely clear. ▪ Rapid expressers included *1/*1B, *1B/*1B, *1/*1G, *1G/*1G. Poor expressers = *1/*22+ *22/*22. Intermediate = *1B/*22. Normal = *1/*1. |
| *CYP3A4*22 (G > A) (rs35599367)* | Deininger 2016 [9] | 76 | 44 ± 14 | NR | Caucasian 81.6% African American 3.9% Asian or Pacific Islander 6.6% American Indian, Eskimo, or Aleutian 1.3% Other 6.6% | NR | Yes | TAC + MMF (77.6%), PRED (23.7%), AZA (13.2%) or SIR (10.5%) | ▪ The unadjusted mean TAC C0/D was 21% higher and TAC TDD was 8% lower in CYP3A4*1/*22 heterozygotes vs. CYP3A4*1/*1 homozygotes, but these results were not statistically significant. ▪ The mean (95% CI) TAC C0 did not differ significantly between CYP3A4*1/*1 [6.5 (5.9–7.2) ng/mL] vs. CYP3A4*1/*22 [7.5 (5.0–11.2) ng/mL, $p$= 0.33]. |
| *CYP3A4*22* | Gijsen 2013 | 60 | Median = 4 | NR | Caucasian 65.0% | NR | Yes | TAC + MMF + | ▪ CYP3A4*22 carriers required 30% less TAC ($p$ = 0.016) to |

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| *(G > A) (rs35599367)* | [3] | | IQR = 12 | | African American 6.7% Asian 5.0% Native 1.7% Unknown 21.6% | | | CORT | achieve similar target concentrations compared to CYP3A4*1/*1 carriers.<br>▪ CYP3A poor metabolizers (CYP3A5*3/*3 + CYP3A4*22) required 17% ($p$ = 0.023) less TAC dose than intermediate metabolizers (CYP3A5*3/*3 + CYP3A4*1/*1) and 48% less ($p$ < 0.0001) than extensive metabolizers (CYP3A5*1 + CYP3A4*1/*1).<br>▪ Poor metabolizers had dose-adjusted concentrations 18% higher than intermediate metabolizers ($p$ = 0.35) and 193% higher than extensive metabolizers ($p$ < 0.0001).<br>▪ eGFR at last available serum creatinine concentration was not different between CYP3A4*1/*1 homozygotes (128.7 [IQR: 82.1] mL/min/1.73 m$^2$) and CYP3A4*22 allele carriers (154.9 [IQR: 150.5] mL/min/1.73 m$^2$; $p$ = 0.6). |
| *CYP3A4*22 (G > A) (rs35599367)* | Liu 2024 [5] | 177 | 54 | NR | Unknown (USA) | NR | NR | TAC | ▪ CYP3A4 rapid expressers had 44 and 57% lower median TAC C0/D (CYP3A4 *1/*22 + *22/*22) compared to normal expressers and poor/intermediate expressers, respectively, from POD 2 to discharge ($p$ < 0.0005). |
| | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95% Asian 3% Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | - Dose-adjusted trough concentration (C0): no significant differences. |
| *CYP3A4*1G (20230G > A) (rs2242480)* | Liu 2022 [7] | 66 | Median = 10 IQR = 7m–17y | NR | Unknown (China) | NR | Yes | TAC + MMF + PRED | ▪ The C0/D ratio in wild-type CYP3A4*1G (*1/*1) patients was approximately 1.7-fold higher than that in those carrying at least one mutant allele (*1/*G and *G/*G) (136.10 ± 74.69 vs. 79.85 ± 37.89 ng/mL per mg/kg/d, $p$ = 0.0031).<br>▪ Patients with CYP3A4*1G mutation required 1.3-fold higher doses than wild-type patients (0.1856 ± 0.1015 vs. 0.1427 ± 0.1146 mg/kg/d, $p$ = 0.0057).<br>▪ No correlation between CYP3A4*1G genotype and acute renal failure. |
| *CYP3A4*1G (20230G > A) (rs2242480)* | Liu 2024 [5] | 177 | 54 | NR | Unknown (USA) | NR | NR | TAC | ▪ *1B reported as c-392G > A and rs2740574 and *1G as c1026 + 12G > A and rs2242480 but which variant is star allele is not completely clear.<br>▪ Rapid expressers included *1/*1B, *1B/*1B, *1/*1G, *1G/*1G. Poor expressers = *1/*22+ *22/*22. Intermediate = *1B/*22. Normal = *1/*1. |
| ***CYP3A5*** | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| *G > A* | Antignac 2010 [25] | 60 | NR | NR | NR | NR | NR | EVE | ▪ PK model: no influenced CL/F and V/F |
| *CYP3A5*3/*1 6986A > G rs776746* | Lemaitre 2012[26] | 59 | 50 ± 14 (17–80) | NR | NR (France) | NR (France) | NR | EVE + TAC or CSA + MMF or AZA + CORT | ▪ PK: CYP3A5 *1/*1 and *1/*3 patients (expressors) appeared to be higher, but not significantly than those of CYP3A5 *3/*3 (non-expressors) |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | No | CSA or TAC | ▪ Renal function: no significant differences |
| | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95% Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: CYP3A5*1/*3 variant required higher EVE dose of 0.02 mg/kg/day than CYP3A5*3/*3 to reach the targeted C0. |
| *CYP3A5 (-A392G) (rs776746)* | Díaz-Molina 2012 [23] | 65 | 54.55 ± 10 | NR | Unknown (Spain) | NR | NR | TAC + MMF + PRED | ▪ Patients with CYP3A5 *3/*3 required lower doses than those with CYP3A5*1/*3 at 12 months (0.08 ± 0.10 vs. 0.14 ± 0.03 mg/kg/day, $p < 0.001$). Differences were seen at 1 week and 6 months but were not significant.<br>▪ Patients with CYP3A5*3/*3 had a higher concentration/dose ratio than those with CYP3A5*1/*3 at 6 months (185 ± 101.9 vs. 68.11 ± 53.89 ng/mL/mg/kg/d, $p = 0.045$) and at 12 months (205.76 ± 109.67 vs. 84.71 ± 46.57 ng/mL/mg/kg/d, $p = 0.005$). At 1 week, a difference was seen but was not significant.<br>▪ CYP3A4 expression was not associated with the frequency of new-onset diabetes after transplant. |
| *CYP3A5*1 (T > C) (rs776746)* | Mirza 2021 [28] | 66 (Poor: 41 Inter: 21 Exten:4) | Poor (Median = 58 IQR = 55–65) Inter (Median = 63 IQR = 60–67) Exten (Median = 58 IQR = 55–62) | NR | Poor (Caucasian 80.5% Hispanic/Latino 4.9% African American 12.2% Other 2.4%) Inter (Caucasian 43% Hispanic/Latino 24% African American 33%) Exten (African American | NR | NR | TAC ± MMF ± AZA | ▪ No statistically significant differences in starting TAC dose (median [IQR]): non-CYP3A5*1 0.02 [0.02–0.05] mg/kg/day, CYP3A5*1 heterozygous 0.03 [0.02–0.05] mg/kg/day and CYP3A5*1 homozygous 0.02 [0.02–0.02] mg/kg/day ($p = 0.17$).<br>▪ Significantly higher first therapeutic doses in extensive and intermediate compared to poor ($p = 0.01$).<br>▪ Significantly lower stable therapeutic doses in poor compared to intermediate and extensive ($p < 0.001$). |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | 100%) | | | | | |
| *CYP3A5*1 (T > C) (rs776746)* | Uno 2018 [8] | 65 (*1/*1: 5 *1/*3: 22 *3/*3: 38) | *1/*1 y *1/*3 Median = 43 IQR = 30–55<br>*3/*3 Median = 40 IQR = 29–47.8 | NR | Unknown (Japan) | NR | Yes | TAC + MMF + AZA | ▪ Before clotrimazole discontinuation: significant differences in dose/weight (0.052 vs. 0.035 mg/kg/day, $p$ = 0.0012), C0/dose/weight (201.3 vs. 302.8 ng/mL/mg/kg/day, $p$ = 0.001), and AUC0–12 (205.4 vs. 179.1 ng*h/mL, $p$ = 0.0034) between CYP3A5 expression and non-expression.<br>▪ After clotrimazole discontinuation: significant differences in dose/weight (0.156 vs. 0.068 mg/kg/day, $p$ = 0.0004), C0/dose/weight (73.0 vs. 163.7 ng/mL/mg/kg/day, $p$ = 0.0004), AUC0–12/dose/weight (1121.5 vs. 2532.4 ng*h/mL/mg/kg/day, $p$ = 0.0001) and CL/F (0.89 vs. 0.39 L/h/kg, $p$ = 0.0001) between CYP3A5 expression and non-expression.<br>▪ Median CL/F after clotrimazole discontinuation was 3.3-fold (0.89 vs. 0.27 L/h/kg, $p$ = 0.002) and 2.2-fold (0.39 vs. 0.18 L/h/kg, $p$ < 0.0001) higher than before discontinuation of clotrimazole in the CYP3A5 expresser and non-expressor groups, respectively.<br>▪ The median AUC0–12/dose/weight before discontinuation of clotrimazole was 3.3-fold (3745.9 vs. 1121.5 ng h/mL/mg/kg/day, $p$ = 0.002) and 2.2-fold (5453.8 vs. 2532.4 ng h/mL/mg/kg/day, $p$ < 0.0001) higher than after discontinuation of clotrimazole in the CYP3A5 expresser and non-expressor groups, respectively.<br>▪ No significant differences in concentrations at any sampling time between the CYP3A5 expresser and non-expressor groups before and after discontinuation of clotrimazole. |
| *CYP3A5*1 (T > C) (rs776746)* | Uno 2019 [29] | 26 (*1/*1: 2 *1/*3: 8 *3/*3: 16) | *1/*1 y *1/*3 Median = 45.1 IQR = 14.8<br>*3/*3 Median = 44.3 IQR = 11.8 | NR | Unknown (Japan) | NR | Yes | TAC + MMF + AZA | ▪ After discontinuation of clotrimazole: CYP3A5-expressing group (*1/*1 or *1/*3) had a mean 3.3-fold increase in apparent oral clearance of TAC (0.27 vs. 0.89 L/h/kg, $p$ = 0.002) compared to the CYP3A5-non-expressing group (*3/*3) with a mean 2.2-fold increase (0.18 vs. 0.39 L/h/kg, $p$ < 0.0001).<br>▪ Significant correlations between C0 and TAC were observed after discontinuation of clotrimazole in the CYP3A5-expressing and non-expressing groups, respectively ($R^2$ = 0.49 and 0.42, all $p$ < 0.05), but not before discontinuation of clotrimazole. |
| *CYP3A5*3 (T > C)* | Zheng 2003 [6] | 54 | CYP3A5 *1/*3: 8.7 ± 1.7 | NR | CYP3A5: African American: | NR | NR | TAC + PRED ± MMF/AZA | ▪ At 3 months, significant differences in TAC levels per dose/kg/day were found between CYP3A5 *1/*3 vs. *3/*3 |

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| *(rs776746)* | | | CYP3A5 *3/*3: 7.2 ± 1.2 | | 5.6% Other: 94.4% | | | | (29.2 ± 27.7 vs. 57.7 ± 48.9, $p = 0.014$).<br>▪ At 6 months, significant differences in TAC levels per dose/kg/day were found between CYP3A5 *1/*3 vs. *3/*3 (31.0 ± 23.5 vs. 65.8 ± 79.7, $p = 0.017$).<br>▪ At 12 months, significant differences in TAC levels per dose/kg/day were found between CYP3A5 *1/*3 vs. *3/*3 (33.1 ± 21.6 vs. 65.4 ± 72.6, $p = 0.015$). |
| *CYP3A5*3 (T > C) (rs776746)* | Deininger 2016 [9] | 76 | 44 ± 14 | NR | Caucasian 81.6% African American 3.9% Asian or Pacific Islander 6.6% American Indian, Eskimo, or Aleutian 1.3% Other 6.6% | NR | Yes | TAC + MMF (77.6%), PRED (23.7%), AZA (13.2%) or SIR (10.5%) | ▪ Unadjusted mean TAC C0/D was 1.8-fold lower ($p < 0.001$) and TDD was 2-fold higher ($p < 0.001$) in CYP3A5 expressers vs. non-expressers.<br>▪ Mean (95% CI) TAC C0 did not differ significantly between CYP3A5*1/*1 or CYP3A5*1/*3 [7.2 (6.2–8.5) ng/mL] vs. CYP3A5*3/*3 [6.5 (5.8–7.3) ng/mL, $p = 0.37$]. |
| *CYP3A5*3 (6986A > G) (rs776746)* | Déri 2021 [30] | 78 | 53.1 (range:19.5–68.7) | NR | Unknown (Hungary) | NR | NR | TAC + MMF + CORT | ▪ 3 groups: CYP3A5 expression (*1/*3 or *1/*1), CYP3A5 non-expression (*3/*3) with low CYP3A4, and CYP3A5 non-expression (*3/*3) with normal CYP3A4.<br>▪ 15-day TAC concentration: CYP3A5 expression (48.3 ± 13.57 (ng/mL)/(mg/kg)) CYP3A4 normal expression (92.6 ± 11.33 (ng/mL)/(mg/kg)); CYP3A4 low expression (192.5 ± 63.60 (ng/mL)/(mg/kg); $p < 0.0001$).<br>▪ TAC dose to reach 15-day levels: CYP3A5 expression (0.240 ± 0.081 mg/kg); normal CYP3A4 expression (0.138 ± 0.0283 mg/kg), low CYP3A4 expression (0.080 ± 0.0266 mg/kg, $p < 0.0001$).<br>▪ For recipients carrying the wild-type CYP3A5*1 allele, a markedly higher dose of TAC (2.4-fold) was required for the target blood concentration; for those expressing normal CYP3A4, the required dose was 30–40% higher; and for those expressing low CYP3A4, the required dose was approximately 20% lower than recommended. |
| *CYP3A5*3 (T > C) (rs776746)* | Gijsen 2011 [31] | 39 | Median = 6 IQR = 13.75 | NR | White 71.8% African American 5.1% Asian 10.3% Unknown 12.8% | NR | Yes | TAC ± MMF ± CORT | CYP3A5 expressers:<br>▪ Require higher TAC dose (median and IQR): 0.14 [0.09] vs. 0.06 [0.04] mg/kg/12h ($p = 0.001$);<br>▪ Had lower concentration/dose ratio (median and IQR): 45.34 [44.54] vs. 177.78 [145.38] ng/mL per mg/kg/12h ($p < 0.0001$);<br>▪ Age and CYP3A5 genotype predict TAC dose requirements |

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| | | | | | | | | | and concentration/dose ratio ($R^2$ = 0.351, $p$ = 0.001 and $R^2$ = 0.521, $p < 0.001$);<br>▪ No relationship between CYP3A5 genotype and estimated glomerular filtration rate: expressers (median 125.37 [IQR, 56.77] mL/min/1.73 $m^2$) vs. non-expressers (median 130.43 [IQR, 72.65] mL/min/1.73 $m^2$), $p$ = 0.941). |
| *CYP3A5*3 (T > C) (rs776746)* | Gijsen 2013 [3] | 60 | Median = 4<br>IQR = 12 | NR | Caucasian 65.0%<br>African American 6.7%<br>Asian 5.0%<br>Native 1.7%<br>Unknown 21.6% | NR | Yes | TAC + MMF + CORT | ▪ CYP3A poor metabolizers (CYP3A5*3/*3 + CYP3A4*22) required 17% ($p$ = 0.023) less TAC dose than intermediate metabolizers (CYP3A5*3/*3 + CYP3A4*1/*1) and 48% less ($p < 0.0001$) than extensive metabolizers (CYP3A5*1 + CYP3A4*1/*1).<br>▪ Poor metabolizers showed 18% higher dose-adjusted concentrations than intermediate metabolizers ($p$ = 0.35) and 193% higher than extensive metabolizers ($p < 0.0001$). |
| *CYP3A5*3 (T > C) (rs776746)* | Kniepeiss 2011 [10] | 45 (TAC 15 + EVE 30) | TAC *3*3<br>54 ± 11<br>TAC *3*1<br>37 ± 3<br>EVE *3*3<br>47 ± 14<br>EVE *3*1<br>60 ± 8 | NR | Caucasian 100% | NR | Yes | TAC/CSA + MMF + PRED<br><br>EVE + CSA+ PRED | TAC:<br>▪ Average TAC dose significantly higher in subjects expressing CYP3A5 compared to non-expressors:<br>o 2-month dose: non-expressors 5.9 ± 3.3 vs. expressors 15.5 ± 0.7 mg/day, $p < 0.05$;<br>o 12-month dose: non-expressors 4.8 ± 2.6 vs. expressors 11.0 ± 1.4 mg/day, $p < 0.05$;<br>o 36-month dose: non-expressors 4.4 ± 1.9 vs. expressers 12.0 ± 2.8 mg/day, $p < 0.05$.<br>EVE:<br>▪ Neither dose nor levels of everolimus were significantly different between CYP3A5 expressers and non-expressors. |
| *CYP3A5*3 (A > G) (rs776746)* | Liu 2019 [32] | 55 | *1/*3 (27.3%)<br>39.20 ± 11.73<br>*1/*1 (72.7%)<br>40.92 ± 14.26 | NR | Unknown (China) | NR | Yes | TAC + MMF + PRED | ▪ CYP3A5*3/*3 expressers had significantly higher TAC C/D than CYP3A5*1/*3 expressers (median with IQR):<br>o 1 month: 273.32 (208.27–383.29) vs. 132.27 (98.22–155.88) ng/mL per mg/kg, $p < 0.001$;<br>o 3 months: 261.00 (188.65–357.50) vs. 90.87 (66.34–131.89) ng/mL per mg/kg, $p < 0.001$;<br>o 6 months: 343.33 (217.75–425.60) vs. 115.16 (95.06–139.57) ng/mL per mg/kg, $p < 0.001$ mg/kg, $p < 0.001$;<br>o 1 year: 341.55 (256.68–491.87) vs. 110.20 (80.32–167.66) ng/mL per mg/kg, $p < 0.001$;<br>o 2 years: 316.88 (210.38–474.69) vs. 106.04 (89.56–172.38) ng/mL per mg/kg, $p < 0.001$; |

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| | | | | | | | | | ○ 3 years: 311.18 (187.61–495.65) vs. 92.85 (77.25–162.16) ng/mL per mg/kg, $p < 0.001$.<br>▪ The TAC doses (mg/kg) required to achieve the desired concentrations were always lower in the group CYP3A5*3/*3 than in the *1/*3 group within 3 years after transplant (median with IQR):<br>○ 1 month: 0.045 (0.035–0.066) vs. 0.093 (0.071–0.110) mg/kg, $p < 0.00$;<br>○ 3 months: 0.043 (0.035–0.059) vs. 0.096 (0.073–0.110) mg/kg, $p < 0.001$;<br>○ 6 months: 0.037 (0.028–0.051) vs. 0.090 (0.081–0.110) mg/kg, $p < 0.001$;<br>○ 1 year: 0.034 (0.024–0.045) vs. 0.081 (0.073–0.116) mg/kg, $p < 0.001$;<br>○ 2 years: 0.027 (0.021–0.041) vs. 0.080 (0.060–0.100) mg/kg, $p < 0.001$;<br>○ 3 years, 0.029 (0.021–0.040) vs. 0.074 (0.053–0.099) mg/kg, $p < 0.001$.<br>▪ No significant differences in acute rejections between the two groups within 6 months after transplant.<br>▪ CYP3A5 expressers tend to have higher mortality than non-expressors (20% vs. 12.5%, log rank: $p = 0.314$). |
| *CYP3A5*3 (6986A > G) (rs776746)* | Liu 2022 [7] | 66 | Median = 10<br>IQR = 7m–17y | NR | Unknown (China) | NR | Yes | TAC + MMF + PRED | ▪ No correlation CYP3A4*1G genotype and acute kidney failure.<br>▪ The C0/D ratio in CYP3A5 non-expressers (*3/*3) was significantly 2.0-fold higher than that in CYP3A5 expressers (*1/*1 and *1/*3) (133.66 ± 72.18 vs. 65.51 ± 35.80 ng/mL per mg/kg/d, $p < 0.0001$).<br>▪ The dose requirement in CYP3A5 expressers (*1/*1 and *1/*3) was 1.5-fold higher than in non-expressers (*3/*3) (0.1921 ± 0.0991 vs. 0.1298 ± 0.1140 mg/kg/d, $p = 0.0001$).<br>▪ No correlation between CYP3A4*1G genotype and acute renal failure |
| *CYP3A5*3 (rs776746) CYP3A5*6 (rs10264272) CYP3A5*7 (rs41303343)* | Pasternak 2021 [33] | 37 | 9.2 ± 6.3 | NR | White 81.1%<br>Black/African American 10.8%<br>Other 8.1% | NR | NR | TAC ± UNKNOWN | ▪ CYP3A5 phenotype (1 or 0 variant alleles) was significantly associated with increased TAC dose changes (coefficient (slope) 10.59 (95%CI 1.99–19.19), $p = 0.017$) and increased TAC concentrations (coefficient (slope) 27.64 (95%CI 6.48–48.80), $p = 0.012$).<br>▪ CYP3A5 phenotype was associated with increased hospital |

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| | | | | | | | | | stay, intensive care, and total charges.<br>▪ CYP3A5 phenotype was not significantly associated with time to develop biopsy-proven acute rejection or de novo donor-specific antibodies ($p = 0.268$). |
| *CYP3A5*3 (rs776746)*<br>*CYP3A5*6 (rs10264272)*<br>*CYP3A5*7 (rs41303343)* | Pasternak 2023 [34] | 38 | 12.2 ± 4.1 | NR | White 76.3%<br>African American 13.2%<br>Other/unknown 10.5% | NR | NR | TAC + MMF/AZA + CORT | ▪ No statistically significant differences in initial or therapeutic dose between expressers and non-expressers. |
| **1*<br>**1/*3*<br>*6986 A > G *3 (rs776746)* | De Denus 2011 [11] | 160 | 53.2 (IQR: 43.5–58.2) | NR | Caucasian 98.1% | NR | Yes | CSA/TAC/MMF/AZA + CORT | ▪ CSA/TAC concentrations: no significant difference.<br>▪ eGFR: Strongly associated ($p = 0.004$). After adjusting for independent predictors, association remained ($p = 0.002$), with CYP3A5*1 having a higher eGFR at discharge ($p = 0.03$), sustained throughout follow-up. The association was apparent with CSA or TAC at discharge ($p = 0.05$ for both subgroups). |
| | Klauke 2008 [35] | 106 | RI (n = 53): 50.2 ± 14.6<br>noRI (n = 53): 51.3 ± 10.7 | RI (n = 53): 35.5 ± 13.7<br>noRI (n = 53): 34.2 ± 12.1 | NR | NR | NR | CSA/TAC + AZA/MMF + CORT ± mTOR | ▪ Renal function: no significant differences. |
| *6986 A > G *3 (rs776746)* | Herrero 2010 [2] | 18 | NR | NR | NR | NR | NR | CSA / TAC | ▪ *Cmin: variant genotypes showed increases compared with the wild-type genotypes.* |
| | Isla 2009 [24] | 30 | 43 ± 14 | NR | Caucasian | NR | Yes | CSA ± AZA/MMF/CORT/ SIR ± BSX/ATG | ▪ - CSA AUC(0–12h), Cmax, tmax, Css: no significant differences. |
| | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: no significant differences.<br>*For TAC: levels were much higher ( > 100% at 8 months after transplantation) among the GG genotype compared with the GA and even more compared with the AA genotype.* |
| | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95%<br>Asian 3%<br>Other 2% | NR | Yes | TAC/CSA/EVE/SIR + AZA/MMF + CORT | ▪ Dose-adjusted trough concentration (C0): lower for TAC in CYP3A5 expressors at all studied time points ($p \leq 0.002$) and required 2.2- to 2.6-fold higher dose to reach the targeted concentration compared with non-expressors.<br>-Rejection: no differences (TAC).<br>-eGFR: no differences (TAC). |

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| | Sigurdardottir 2013 [16] | 107 | NR | NR | NR | NR | NR | TAC or CSA | ▪ Dose-adjusted trough levels: TAC group carriers of *1/*3 required significantly higher doses at 1, 3, and 6 months post-transplantation compared to *3/*3. For CSA group, only was found statistical difference at 6 months post-transplantation ($p = 0.043$).<br>-Rejection: no significant differences. |
| *267871 G > A *6 (rs10264272)* | Herrero 2010 [2] | 18 | NR | NR | NR | NR | NR | CSA / TAC | ▪ *Cmin: variant genotypes showed increases compared with the wild-type genotypes.* |
| | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: no significant differences.<br>*For CSA: the nonfunctional allele (A) seemed to be associated with a trend for higher blood drug levels.* |
| ***CYP2C8*** | | | | | | | | | |
| *CYP2C8*1, CYP2C8*3* | Kniepeiss 2013 [12] | 30 | *1/*1<br>47 ± 16<br>*1/*3<br>52 ± 8 | NR | NR (Austria) | NR (Austria) | Yes | EVE + CSA + CORT (previously CNI + MMF + CORT) | ▪ PK: no influence on dose requirements or levels of everolimus.<br>▪ Rejection: no influence.<br>▪ Infections: no influence. |
| | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.-635_-634 delAT rs372775254* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.-411T > C rs7912549* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.-370T > G CYP2C8*1C rs17110453* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.-271C > A CYP2C8*1B rs7909236* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.332-6_332-5InsT rs11572078* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.332-64G > A rs2275622* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.416G > A (p.Arg139Lys) CYP2C8*3 rs11572080* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *c.1196A > G* | Lesche 2015 | 37 | 53 (16–75) | NR | Caucasian 95% | NR | Yes | EVE + MMF or | ▪ PK: no influence on EVE trough concentration. |

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| *(p.Lys399Arg) CYP2C8*3 rs10509681* | [14] | | | | Other 5% | | | AZA + CORT | |
| *c.1291 + 106G > A rs1934951* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95% Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| ***POR*** | | | | | | | | | |
| *c.1508C > T (p.Ala503Val) POR*28 rs1057868* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95% Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| **28 (rs1057868)* | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95% Asian 3% Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | ▪ Dose-adjusted trough concentration (C0): higher for TAC in variant carriers at all time points, resulting in significant differences at 3 ($p$ = 0.025) and 6 months ($p$ = 0.047) after HTx. |
| | Sigurdardottir 2013 [16] | 107 | NR | NR | NR | NR | NR | TAC or CSA | ▪ *Dose-adjusted trough levels: TAC dose requirement was influenced by *28 variant at months 3 and 6.* |
| *POR (6593A > G) (rs2868177)* | Liu 2022 [7] | 66 | Median = 10 IQR = 7m–17y | NR | Unknown (China) | NR | Yes | TAC + MMF + PRED | ▪ No statistically significant differences between POR genotype and concentration/dose ratio. ▪ No statistically significant differences between POR genotype and dose. ▪ No correlation between CYP3A4*1G genotype and acute renal failure. |
| ***NR1I2 NR112/PXR*** | | | | | | | | | |
| *c.-1135C > T rs3814055* | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95% Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| *G25385C > T (rs3814055)* | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95% Asian 3% Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | ▪ Dose-adjusted trough concentration (C0): no significant differences. |
| | Sigurdardottir 2013 [16] | 107 | NR | NR | NR | NR | NR | TAC or CSA | ▪ *Dose-adjusted trough levels: TAC dose requirement was influenced by T variant at month 1.* |
| **UGT1A9** | | | | | | | | | |
| T > G (rs6731242) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7% African American 10.8% Asian 4.1% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: no difference in the first 12 months post-transplant ($p$ = 0.081). |

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| | | | | | Other 7.4% | | | | |
| **UGT2B7** | | | | | | | | | |
| C802T (rs749366) | Ting 2010 [17] | 32 | 61.3 ((R: 23.2–77.6) | NR | NR | NR | NR | MMF ± CSA/TAC/SIR ± CORT | ▪ AcMPAG AUC(0–12): higher in TT genotype compared with C allele carriers ($p$ = 0.007). |
| **IMPDH2** | | | | | | | | | |
| rs11706052 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: G variant was significantly associated with neutropenia |
| **IMPDH1** | | | | | | | | | |
| rs2288553 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: no influence. |
| rs2288549 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: no influence. |
| rs2278293 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: no influence. |
| rs2278294 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: A variant was significantly associated with gastrointestinal intolerance, leading to drug discontinuation. |
| rs2228075 | Ohmann 2010 [19] | 59 | Pediatric | NR | Caucasian 86% African 10% Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: A variant was significantly associated with gastrointestinal intolerance, leading to drug discontinuation. |
| rs2288553, rs2288549, rs2278293, rs2278294, rs2220875 (H: TCCCC, TCTTT, TTCCC, TCTCC, ACCCC) | Ohmann 2010 [19] | 59 | 8.2 (IQR: 1.9–13.5) | NR | White non-Hispanic 86.4% White Hispanic 3.4% Black non-Hispanic 10.2% | NR | NR | MMF + TAC/CSA | ▪ GI intolerance: Significantly associated with carriers of TCTTT haplotype in comparison with non-carriers ($p$ = 0.005). Significantly associated with TCCCC non-carriers versus carriers ($p$ = 0.055). No significant differences for the rest of haplotypes. |
| A > G (rs11761662) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7% African American 10.8% Asian 4.1% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: no difference in the first 12 months post-transplant ($p$ = 0.087). |

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| | | | | | Other 7.4% | | | | |
| ***TPMT*** | | | | | | | | | |
| A719G<br>G460A<br>G238C | Liang 2013 [22] | 93 | 49.4 | 33.7 | Caucasian | NR | NR | CSA or TAC + AZA | ▪ TPMT activity level: HZ showed lower activity than WT ($p < 0.001$)<br>▪ Rejection: HZ showed earlier severe rejection ($p < 0.001$), greater total rejection ($p = 0.02$), and more frequent AZA discontinuation ($p = 0.01$) than WT.<br>▪ Leukopenia: no differences. |

Abbreviations: SNP, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; CYP, cytochrome P450; A, adenine; G, guanine; C, citosine; T, timine; U, uracil; NR, not reported; TAC, tacrolimus; MMF, mycophenolate mofetil; CORT, corticosteroids; CL/F, apparent plasma clearance of drug after extravascular administration; POD, postoperative day; CL, clearance; PRED, prednisone; CSA, cyclosporine; AZA, azathioprine; SIR, sirolimus; BSX, basiliximab; ATG, anti-thymocyte globulin; AUC, area under the curve; Cmax, concentration maximum; t max, time maximum; Css, concentration stationary state; USA, United States of America; C0/D, initial concentration–dose relationship; TDD, total daily dose; CI, confidence interval; RI, renal insufficiency; ng, nanograms; mL, milliliters; IQR, interquartile range; eGFR, estimated glomerular filtration rate; min, minutes; $m^2$, square meters; C0, initial concentration; m, months; y, years; mg, milligrams; kg, kilograms; d, days; PK, pharmacokinetics; EVE, everolimus; V/F, apparent volume of distribution after extravascular administration; L, liters; h, hours; vs., versus; AUC0–12; area under the curve from 0 to 12 h; $R^2$, coefficient of determination; mTOR, mammalian target of rapamycin; Cmin, concentration minimum; CNI, calcineurin inhibitors; HTx, heart transplantation; POR, cytochrome P450 oxidoreductase; NR1I2, nuclear receptor subfamily 1 group I member 2; PXR, pregnane X receptor; UGT, uridine glycosyltransferase; CMV, citomegalovirus; AcMPAG, acyl glucuronide of mycophenolic acid; IMPDH, inosine monophosphate dehydrogenase; TPMT, thiopurine methyltransferase; HZ, heterozygous; WT, wild type.

### *3.2. Membrane Transporters*

#### 3.2.1. Efflux Transporters

- ATP-binding cassette transporter B family member 1 (ABCB1)

The ABCB1 gene encodes for P-glycoprotein (P-gp), a transmembrane efflux transporter that affects pharmacokinetics of several drugs, including immunosuppressants. P-gp is highly expressed in barrier and excretory tissues cells, such as enterocytes, hepatocytes, or kidney cells. Genetic variations in ABCB1 have been widely studied in the context of transplantation with some variable conclusions about its effects on effectiveness, toxicity, and pharmacokinetics of immunosuppressants (Table 2). The most frequently investigated polymorphisms of the ABCB1 gene include the synonymous single nucleotide polymorphisms (SNPs) 1236C > T (rs1128503) and 3435C > T (rs1045642), along with the nonsynonymous SNP 2677G > T/A (rs2032582). The TT variant genotype associated with these SNPs has been linked to decreased mRNA expression levels and reduced activity of P-gp.

A majority of the reviewed studies explored the association between ABCB1 gene polymorphisms and the pharmacokinetics of CNI. In the context of tacrolimus therapy, several investigations reported that individuals carrying the wild-type ABCB1 genotype exhibited lower blood concentrations of the drug, particularly within the initial two weeks following transplantation in adults [2], and at 6- and 12-month intervals in pediatric recipients [6]. However, other studies that also analyzed the relationship of tacrolimus concentrations with these polymorphisms did not find significant differences [7,11,13,16,23,27,31]. Cyclosporine is likewise transported by P-gp, and multiple studies have reported decreased blood levels of the drug in individuals carrying the wild-type genotype of the ABCB1 gene [2,11,16,24,29,32,33], but other authors did not obtain significant differences [11,13,32]. The variability in the impact of ABCB1 polymorphisms on CNI pharmacokinetics may be attributed to differences in genetic backgrounds among study populations or limitations related to small sample sizes. Nephrotoxicity is related to high concentrations of CNI, so a lower activity of P-gp due to ABCB1 polymorphisms could promote the appearance of immunosuppressant renal toxicity. Most of the studies analyzed did not find significant differences between ABCB1 polymorphisms and renal function. Some authors found statistical differences in renal function for the infrequent rs9282564 polymorphism, where AG genotype was associated with higher CNI blood concentrations of cyclosporine and lower renal function compared to variant genotype [7,11,16,23,27,28,33]. Other polymorphisms analyzed in the same study (including 1236C < T, 3435C < T and 2677G < T/A) were not associated with nephrotoxicity [15].

Other common toxicities of CNI have been analyzed too. In a cohort of 170 adult heart transplant recipients, the presence of wild-type genotypes for the 3435C > T and 2677G > T/A polymorphisms was associated with an increased risk of experiencing acute rejection episodes grade ≥3A. [38], but this association was not achieved in smaller groups [15,36]. One study reported lower frequency in the appearance of gingival growth in wild-type ABCB1 genotypes compared to variant genotypes for 3435C < T polymorphism with significant differences but showed no differences for 2677G < T/A polymorphism [39]. Wild-type ABCB1 genotypes were also related to lower probability of infections and lower frequency of serious infections during the first year post-transplant in several studies [15,23]. Post-transplantation onset of diabetes was not associated with these polymorphisms [23]; neither was steroid dependency after one year post-transplantation [40].

Everolimus is also a substrate of P-gp. Several studies have reported no significant differences in drug blood concentrations in the three most common polymorphisms previously mentioned [26]. However, 3435C < T polymorphism may have an influence on

apparent clearance and apparent volume of distribution [25], and the variant genotype has been associated with everolimus higher blood levels [41].

- ATP-binding cassette transporter B family member 2 (ABCB2)

The ABCC2 gene encodes the organic anion transporter multidrug resistance protein 2 (MRP2), an efflux transporter involved in the elimination of endogenous and exogenous substances. It is also highly expressed in enterocytes, hepatocytes, and kidney cells and ABCC2 genetic polymorphisms can play a significant role in pharmacokinetics and clinical outcomes of immunosuppressant drugs (Table 2). The three most studied genetic variants are c.-24 C > T (rs717620), c.1249 G> A (rs2273697), and c.3972 C > T (rs3740066).

A study analyzed the relationships of the mentioned ABCC2 gene polymorphisms and tacrolimus blood concentrations but found no significant differences between variant genotypes and the wild-type genotype [42].

MRP2 participates in the enterohepatic cycle of mycophenolate acid and its metabolites. In a study of 59 heart transplanted pediatric patients, the variant genotype of polymorphism c.-24 C > T was linked to gastrointestinal intolerance that resulted in the discontinuation of MMF therapy [20]. Other study analyzed the effects of c.-24 C > T and c.3972 C > T variants on MMF clinical outcomes in thoracic transplant recipients reporting anemia (rs3740066) and leukopenia (rs17222723), but results were presented globally, and we could not obtain heart transplant data alone [17].

With respect to the serum concentrations of MPA and its metabolites, two studies failed to identify significant associations with ABCC2 gene polymorphisms [15]. However, in a large pediatric cohort comprising 290 heart transplant recipients, the presence of the wild-type ABCC2 (rs717620) genotype was linked to an elevated risk of both early and late graft rejection, each accompanied by hemodynamic compromise [43].

#### 3.2.2. Efflux Transporters

- Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1)

SLCO1B1 plays a role in the hepatic uptake of MMF (Table 2). In the context of renal transplantation, the presence of the minor allele of the SLCO1B1 (rs4149056) polymorphism has been associated with reduced clearance of MPA compared to the wild-type genotype, likely due to diminished hepatic drug uptake linked to this variant [44]. However, in heart transplant cohort, no influence in MMF pharmacokinetics and toxicity were reported for SLCO1B1 (rs4149056 and rs2306283) and SLCO1A1 (rs11568564, rs72559749, and rs11568563) polymorphisms [15].

- Solute Carrier Family 13 Member 1 (SLC13A1)

SLC13A1 is a gene that encodes the sodium/sulfate co-transporter, which is present in the intestine and kidneys. A cohort of 148 heart transplant recipients identified that variant carriers of rs2140516 polymorphism had an increased risk of leukopenia in the first year post-transplant when treated with mycophenolate and cytomegalovirus antiviral drugs [37].

**Table 2.** Characteristics of the studies included in systematic review for transporter genes.

| SNP | Study | n | Age Recipient (Range) | Age Donor (Range) | Ethnia Recipient | Ethnia Donor | HWE | Immunossuppressant Scheme | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| **ABCB1** | | | | | | | | | |
| C3435T T/T. C/C. C/T (exon 26; rs1045642) | Barnard 2006 [38] | 170 | T/T 50.5 ± 1.6<br>C/C 46.6 ± 2.8<br>C/T 47.2 ± 1.2 | T/T 31.4 ± 1.9<br>C/C 29.2 ± 2.6<br>C/T 32 ± 1.2 | NR | NR | Yes | CSA + AZA + CORT | ▪ Rejection (endomyocardial biopsy-proven rejection (EBPR)): CC homozygous were 1.80 times (1.05–3.09. $p = 0.03$) more likely to undergo a ≥3A rejection episode in the first 12 months than T-.<br>▪ Significant difference in Kaplan–Meier days post-transplant curves of freedom from grade ≥3A rejection ($p = 0.04$). |
| | Chowbay 2003 [45] | 14 | 47.9 ± 9.8 | NR | Chinese 71.4%<br>Indian 28.6% | NR | No | CSA + AZA + CORT | ▪ AUC(0–4h), AUC(0–12h), Cmax, and Cmin: no significant differences. |
| | De Denus 2011 [11] | 160 | 53.2 (RIC: 43.5–58.2) | NR | Caucasian 98.1% | NR | Yes | CSA/TAC/MMF/AZA + CORT | ▪ CSA/TAC concentrations: no significant difference.<br>▪ eGFR: no significant difference. |
| | Díaz-Molina 2012 [23] | 65 | 54.55 ± 10 | NR | Unknown (Spain) | NR | NR | TAC + MMF + PRED | ▪ ABCB1 expression was not associated with TAC concentrations.<br>▪ ABCB1 expression was not associated with the frequency of new-onset diabetes after transplantation. |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60%<br>Black 13%<br>Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| | De Iudicibus 2008 [39] | 50:<br>Heart 21<br>Renal 26<br>Lung 4 | Overgrowth (mix)<br>< 30% 56.3 (34–73)<br>≥ 30% 57.9 (35–75) | NR | NR | NR | NR | CSA | ▪ Gingival overgrowth (mix): 3435TT genotype was significantly more frequent in the group with clinically significant gingival overgrowth (OR = 7.5. 95% CI = 1.323–42.52; $p = 0.019$). |
| | Herrero 2010 [2] | 18 | NR | NR | NR | NR | NR | CSA / TAC | ▪ Cmin TAC/CSA: wild-type genotype tended to stabilize drug levels within the therapeutic range during the first 3 months post-transplantation; variant genotype was associated with an increased blood level between the first and the second week. |
| | Isla 2009 [24] | 30 | 43 ± 14 | NR | Caucasian | NR | Yes | CSA ± | ▪ CSA AUC(0–12h), Cmax, tmax, Css: T presented |

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| | | | | | | | | AZA/MMF/CORT/ SIR ± BSX/ATG | greater values of AUC0–12 ($p$ = 0.01) and of Css ($p$ = 0.05) in comparison to CC carriers. No other significant differences were found. |
| | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95% Asian 3% Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | ▪ Dose-djusted trough concentration (C0): no significant differences. |
| | Taegtmeyer 2010 [40] | 337 | 48.1 ± 11.1 | 32.5 ± 13.2 | White 90.5% | NR | Yes | CSA ± AZA ± CORT ± ATG | ▪ Trough CSA concentration and dose- and weight-adjusted CSA trough concentration: no significant differences.<br>▪ Time to first endomyocardial biopsy-proven acute rejection episode (grade 3A): no significant differences.<br>▪ Weaning from steroids at 1 year post-transplantation: no significant differences.<br>▪ Renal function at 1 year post-transplantation: no significant differences. |
| | Liu 2022 [7] | 66 | Median = 10 IQR = 7m–17y | NR | Unknown (China) | NR | Yes | TAC + MMF + PRED | ▪ No statistically significant differences between ABCB1 genotype and concentration/dose ratio.<br>▪ No statistically significant differences between ABCB1 genotype and dose.<br>▪ No correlation between CYP3A4*1G genotype and acute renal failure. |
| C3435T rs1045642 | Antignac 2010 [25] | 60 | NR | NR | NR | NR | NR | EVE | ▪ PK model: ABCB1 genotype influenced CL/F and V/F decreased the objective function value and improved graphical analysis. |
| | Lemaitre 2012 [26] | 59 | 50 ± 14 (17–80) | NR | NR (France) | NR (France) | NR | EVE + TAC or CSA + MMF or AZA + CORT | ▪ PK: no influence. |
| | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95% Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration. |
| | Kunicki 2016 [41] | 31 | 55 (24–76) | NR | NR (Poland) | NR (Poland) | NR | EVE + CNI or MMF | ▪ PK: minor allele T was associated with higher mean dose-normalized EVE trough concentration |
| G2677T A/G. A/T. G/G. G/T. T/T (exon 21; rs2032582) | Barnard 2006 [38] | 170 | A/G 42.5 ± 5.9<br>A/T 52.6 ± 4.5<br>G/G 48.1 ± 2.0<br>G/T 48.9 ±1.3<br>T/T 45.8 ± 2.0 | A/G 36 ± 4.4<br>A/T 42.3 ± 9.6<br>G/G 29.2 ± 1.9<br>G/T 33 ± 1.4<br>T/T 29.3 ± 2.0 | NR | NR | Yes | CSA + AZA + CORT | ▪ Rejection (EBPR): significant difference in the number of ≥3A rejection episodes between the GG group and the TT group ($p$ = 0.038).<br>▪ No differences in Kaplan–Meier days post-transplantation curves of freedom from grade |

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| | | | | | | | | | ≥3A rejection. |
| G2677T A/G. G/G. G/T. T/T (exon 21; rs2032582) | De Denus 2011 [11] | 160 | 53.2 (IQR: 43.5–58.2) | NR | Caucasian 98.1% | NR | Yes | CSA/TAC/MMF/AZA+ CORT | ▪ CSA/TAC concentrations: no difference regarding TAC, but a significant difference regarding CSA concentrations ($p = 0.004$).<br>▪ eGFR: no significant difference. |
| G2677T G/G. G/T. T/T (exon 21; rs2032582) | Chowbay 2003 [45] | 14 | 47.9 ± 9.8 | NR | Chinese 71.4% Indian 28.6% | NR | No | CSA + AZA + CORT | ▪ AUC(0–4h), AUC(0–12h), Cmax, and Cmin: no significant differences. |
| | De Iudicibus 2008 [39] | 50: H21 R26 L4 | Overgrowth (mix) < 30% 56.3 (34–73) ≥ 30% 57.9 (35–75) | NR | NR | NR | NR | CSA | ▪ Gingival overgrowth (mix): no significant differences. |
| | Herrero 2010 [2] | 18 | NR | NR | NR | NR | NR | CSA / TAC | ▪ Cmin TAC/CSA: wild-type genotype tended to stabilize drug levels within the therapeutic range during the first 3 months post-transplantation; variant genotype was associated with an increased blood level between the first and the second week. |
| | Klauke 2008 [35] | 106 | RI (n = 53): 50.2 ± 14.6 noRI (n = 53): 51.3 ± 10.7 | RI (n = 53): 35.5 ± 13.7 noRI (n = 53): 34.2 ± 12.1 | NR | NR | NR | CSA/TAC + AZA/MMF + CORT ± mTOR | ▪ Renal function: no significant differences. |
| | Taegtmeyer 2010 [40] | 337 | 48.1 ± 11.1 | 32.5 ± 13.2 | White 90.5% | NR | Yes | CSA ± AZA ± CORT ± ATG | ▪ Trough CSA concentration: higher in G allele carriers compared with TT genotype at year 3 post-transplantation (GG > GT > TT; $p = 0.03$).<br>▪ Dose- and weight-adjusted CSA trough concentration: no significant differences.<br>▪ Time to first endomyocardial, biopsy-proven acute rejection episode (grade 3A): no significant differences.<br>▪ Weaning from steroids at 1 year post-transplantation: no significant differences.<br>▪ Renal function at 1 year post-transplantation: no significant differences. |
| | Feingold 2012 | 453 | 6.2 ± 6.1 | NR | White 60% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |

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| | [27] | | | | Black 13%<br>Hispanic 23% | | | | |
| | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95%<br>Asian 3%<br>Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | ▪ Dose-adjusted trough concentration (C0): no significant differences. |
| | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence in EVE trough concentration. |
| C1236T C/C. C/T. T/T (exon 12; rs1128503) | Chowbay 2003 [45] | 14 | 47.9 ± 9.8 | NR | Chinese 71.4%<br>Indian 28.6% | NR | No | CSA + AZA + CORT | ▪ AUC(0–4h), AUC(0–12h), Cmax, and Cmin: no significant differences. |
| | Herrero 2010 [2] | 18 | NR | NR | NR | NR | NR | CSA / TAC | ▪ Cmin TAC/CSA: wild-type genotype tended to stabilize drug levels within the therapeutic range during the first 3 months post-transplantation; variant genotype was associated with an increased blood level between the first and the second week. |
| | Jordán 2012 [46] | 60 | NR | NR | NR | NR | NR | CSA or TAC | ▪ AE: Existence of infections ($p = 0.015$) was correlated with this SNP. The variant CC reduces the probability of infections to 50%. |
| | Lesche 2014 [13] | 104 | 47.4 ± 14.3 | NR | White 95%<br>Asian 3%<br>Other 2% | NR | Yes | TAC/CSA/EVE/ SIR + AZA/MMF + CORT | ▪ Dose-adjusted trough concentration (C0): no significant differences. |
| | Lesche 2015 [14] | 37 | 53 (16–75) | NR | Caucasian 95%<br>Other 5% | NR | Yes | EVE + MMF or AZA + CORT | ▪ PK: no influence on EVE trough concentration |
| | Sánchez-Lázaro 2015 [15] | 60 | CSA (n = 36): 53 ± 11<br>TAC (n = 24): 52 ± 10 | CSA (n = 36): 42 ± 12<br>TAC (n = 24): 43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ Serious infection in the first year after transplantation: more frequent in patients carrying the T allele ($p = 0.012$).<br>▪ Blood levels: Statistically lower for CC patients, who presented fewer infections, in months 2 ($p = 0.012$), 10 ($p = 0.025$), and 12 ($p = 0.033$) after transplantation for CSA patients. Same trend observed for TAC patients, although not statistically significant. |
| | Taegtmeyer 2010 [40] | 337 | 48.1 ± 11.1 | 32.5 ± 13.2 | White 90.5% | NR | Yes | CSA ± AZA ± CORT ± ATG | ▪ Trough CSA concentration and dose- and weight-adjusted CSA trough concentration: C allele carriers were higher compared with TT genotype |

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| | | | | | | | | | at year 3 post-transplantation (CC > CT > TT; $p$ = 0.04).<br>▪ Time to first endomyocardial biopsy-proven acute rejection episode (grade 3A): no significant differences.<br>▪ Weaning from steroids at 1 year post-transplantation: no significant differences.<br>▪ Renal function at 1 year post-transplantation: no significant differences. |
| C3435T/G2677T GG/CC, GT/CT, TT/TT (H) | Chowbay 2003 [45] | 14 | 47.9 ± 9.8 | NR | Chinese 71.4%<br>Indian 28.6% | NR | No | CSA + AZA + CORT | ▪ AUC(0–4h), AUC(0–12h), Cmax, and Cmin: no significant differences. |
| | Taegtmeyer 2010 [40] | 337 | 48.1 ± 11.1 | 32.5 ± 13.2 | White 90.5% | NR | Yes | CSA ± AZA ± CORT ± ATG | ▪ Trough CSA concentration: higher in GG/CC haplotype carriers compared with TT/TT haplotype at year 1 post-transplantation ($p$ = 0.02).<br>▪ Dose- and weight-adjusted CSA trough concentration: higher in GG/CC haplotype carriers compared with TT/TT haplotype at year 1 ($p$ = 0.02) and year 5 ($p$ = 0.04) post-transplantation.<br>▪ Time to first endomyocardial biopsy-proven acute rejection episode (grade 3A): no significant differences.<br>▪ Weaning from steroids at 1 year post-transplantation: no significant differences. |
| | Zheng 2003 [6] | C3435 T: 63<br>G2677 T: 63 | C3435T CC: 6.3 ± 6.0<br>C3435T CT/TT: 7.9 ± 7.4<br>G2677T GG: 6.1 ± 5.8<br>G2677T GT/TT: 8.2 ± 7.5 | NR | C3435T:<br>African American: 6.3%<br>Other: 93.7%<br>G2677T:<br>African American: 6.3%<br>Other: 93.7% | NR | NR | TAC + PRED ± MMF/AZA | ▪ Dose- and weight-adjusted trough TAC concentration: No significant differences between G2677T genotypes and C3435T genotypes at 3 months.<br>▪ Dose- and weight-adjusted trough TAC concentration: G2677T GG TAC level was lower than GT/TT at 6 months (35.3 ± 25.1 vs. 72.4 ± 91.7, $p$ = 0.017) and at 12 months (36.4 ± 25.2 vs. 68.4 ± 75.0, $p$ = 0.014).<br>▪ Dose- and weight-adjusted trough TAC concentration: C3435T CC genotype was lower than CT/TT at 6 months (37.0 ± 26.6 vs. 70.8 ± 90.0, $p$ = 0.028) and at 12 months (38.5 ± 25.7 vs. 65.9 ± 74.3, $p$ = 0.033). |

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| C3435T T/T, C/C, C/T G2677T G/G, G/T, T/T C1236T C/C, C/T, T/T (H) | Chowbay 2003 [45] | 14 | 47.9 ± 9.8 | NR | Chinese 71.4% Indian 2.6% | NR | No | CSA + AZA + CORT | ▪ Cmax, Cmin, AUC(0–4h), and AUC(0–12h): CC-GG-CC genotypes (C-G-C haplotypes) had lower values while TT-TT-TT genotypes and the T-T-T haplotypes had higher values. Heterozygote genotype (CT-GT-CT) had intermediate values. |
| | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: more than a 100% increase in CSA levels were observed among CT/CT/GT plus TT/TT/TT carriers at 4 months post-transplantation ($p < 0.05$) with respect to CC/CC/GG carriers. |
| | Taegtmeyer 2010 [40] | 337 | 48.1 ± 11.1 | 32.5 ± 13.2 | White 90.0% | NR | Yes | CSA ± AZA ± CORT ± ATG | ▪ Trough CSA concentration: higher in CC/GG/CC haplotype carriers compared with TT/TT/TT haplotype at year 1 post-transplantation ($p = 0.02$).<br>▪ Dose- and weight-adjusted CSA trough concentration: higher in CC/GG/CC haplotype carriers compared with TT/TT/TT haplotype at year 1 ($p = 0.02$) and year 5 ($p = 0.04$) post-transplantation.<br>▪ Weaning from steroids at 1 year post-transplantation: no significant differences.<br>▪ Renal function at 1 year post-transplantation: no significant differences. |
| ABCB1 (C3435T, G2677T, C1236T) | Gijsen 2011 [31] | 39 | Median = 6 IQR = 13.75 | NR | White 71.8% African American 5.1% Asian 10.3% Unknown 12.8% | NR | Yes | TAC ± MMF ± CORT | ▪ No correlation between ABCB1 genotype and TAC dose or concentration/dose ratio.<br>▪ No correlation between ABCB1 genotype and estimated glomerular filtration rate. |
| ABCB1 (c.1236 C> T) (rs1128503) (c.2677 G> T/A) (rs2032582) (c.3435 C> T) (rs1045642) | Oreschak 2017 [47] | 76 | 53 ± 15 | NR | Caucasian 82% Other 18% | NR | NR | TAC ± UNKNOWN | ▪ TAC titration did not differ significantly between patients with 0 vs. 1 vs. 2 copies of the TTT haplotype (2.72 vs. 2.87 vs. 3.28 ng/mL per mg/day; $p = 0.67$).<br>▪ Total daily TAC dose was similar between TTT haplotype groups (0 copies = 2.43 mg/day, 1 copy = 2.30 mg/day, 2 copies = 2.09 mg/day; $p = 0.78$). |
| rs9282564 | Jordán 2012 [46] | 60 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Renal function: lower renal function in patients AG in contrast to patients AA (25% reduction with $p = 0.04$ for Cockroft, and 32% reduction with $p = 0.002$ for MDRD). |

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| | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: significant difference at month 4 ($p < 0.01$) between AA and AG variants for CSA. |
| | Sánchez-Lázaro 2015 [15] | 60 | CSA (n = 36): 53 ± 11<br>TAC (n = 24): 52 ± 10 | CSA (n = 36): 42 ± 12<br>TAC (n = 24): 43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ Renal function (MDRD): higher for AA carriers compared with AG carriers ($p = 0.001$).<br>▪ Blood levels: AG patients showed higher CSA levels with statistical significance in month 2 after transplantation ($p = 0.002$). TAC showed the same tendency but without statistical differences. |
| rs2235013 | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: G alleles showed linkage to increased CSA levels (50%) over the first 4 months post-transplantation. |
| rs2235033 | Jordán 2011 [36] | 41 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Cmin: T alleles showed linkage to increased CSA levels (50%) over the first 4 months post-transplantation. |
| **ABCC2** | | | | | | | | | |
| rs717620 (G > A) | Ohmann 2010 [20] | 59 | Pediatric | NR | Caucasian 86%<br>African 10%<br>Hispanic 3% | NR | Yes | MMF + TAC or CSA + CORT | ▪ Toxicity: A variant was significantly associated with gastrointestinal intolerance, leading to drug discontinuation. |
| | Burckart 2014 [43] | 290 | Pediatric | NR | Caucasian 74%<br>African 19%<br>Other 7% | NR | Yes | MMF ± UNKNOWN | ▪ RHC: RHC and late RHC were associated with the GG genotype (hazard ratios: 1.80 and 4.57, $p < 0.05$). |
| ABCC2 (c.-24 C > T) (rs717620) (c.1249 G > A) (rs2273697) (c.3972 C > T) (rs3740066) | Oreschak 2018 [42] | 89 | 54 ± 15 | NR | Caucasian 83%<br>Other 17% | NR | NR | TAC ± UNKNOWN | ▪ Level-adjusted dose did not differ significantly between wild type and variants for any polymorphism (c.-24: 2.74 vs. 2.75 ng/mL per mg/day, $p = 0.96$; c.1249: 2.62 vs. 2.98 ng/mL per mg/day, $p = 0.22$; c.3972: 2.94 vs. 2.59 ng/mL per mg/day, $p = 0.18$).<br>▪ Total daily dose did not differ significantly between wild type and variants for any polymorphism (c.-24: 2.47 vs. 2.60 mg/day, $p = 0.65$; c.1249: 2.72 vs. 2.20 mg/day, $p = 0.07$; c.3972: 2.41 vs. 2.63 mg/day, $p = 0.43$). |
| **SLCO1B1** | | | | | | | | | |
| rs4149056 | Sánchez-Lázaro 2015 [15] | 60 | CSA (n = 36): 53 ± 11<br>TAC (n = 24): 52 ± 10 | CSA (n = 36): 42 ± 12<br>TAC (n = 24): 43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ PK: no influence on CSA or TAC trough concentration.<br>▪ Renal function (MDRD): no influence<br>▪ Toxicity: no influence. |
| rs2306283 | Sánchez-Láza | 60 | CSA (n = 36): | CSA (n = 36): | NR | NR | NR | CSA or TAC + | ▪ PK: no influence on CSA or TAC trough |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ro 2015 [15] | | 53 ± 11<br>TAC (n = 24):<br>52 ± 10 | 42 ± 12<br>TAC (n = 24):<br>43 ± 9 | | | | MMF + CORT | concentration.<br>▪ Renal function (MDRD): no influence.<br>▪ Toxicity: no influence. |
| **SLCO1A2** | | | | | | | | | ▪ |
| rs11568564 | Sánchez-Láza ro 2015 [15] | 60 | CSA (n = 36):<br>53 ± 11<br>TAC (n = 24):<br>52 ± 10 | CSA (n = 36):<br>42 ± 12<br>TAC (n = 24):<br>43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ PK: no influence on CSA or TAC trough concentration.<br>▪ Renal function (MDRD): no influence.<br>▪ Toxicity: no influence. |
| rs72559749 | Sánchez-Láza ro 2015 [15] | 60 | CSA (n = 36):<br>53 ± 11<br>TAC (n = 24):<br>52 ± 10 | CSA (n = 36):<br>42 ± 12<br>TAC (n = 24):<br>43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ PK: no influence on CSA or TAC trough concentration.<br>▪ Renal function (MDRD): no influence.<br>▪ Toxicity: no influence. |
| rs11568563 | Sánchez-Láza ro 2015 [15] | 60 | CSA (n = 36):<br>53 ± 11<br>TAC (n = 24):<br>52 ± 10 | CSA (n = 36):<br>42 ± 12<br>TAC (n = 24):<br>43 ± 9 | NR | NR | NR | CSA or TAC + MMF + C | ▪ PK: no influence on CSA or TAC trough concentration.<br>▪ Renal function (MDRD): no influence.<br>▪ Toxicity: no influence. |
| **SLC13A1** | | | | | | | | | |
| T > C (rs2140516) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7%<br>African American 10.8%<br>Asian 4.1%<br>Other 7.4% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: associated with leukopenia in the first 12 months post-transplant, with variant carriers having higher odds compared to wild-type homozygotes ($p < 0.05$). |

Abbreviatures: SNP, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; ABCB1, ATP-binding cassette transporter B family member 1; A, adenine; G, guanine; C, citosine; T, timine; U, uracil; NR, not reported; CSA, cyclosporine; AZA, azathioprine; CORT, corticosteroids; AUC0–4; area under the curve from 0 to 4 h; AUC0–12; area under the curve from 0 to 12 h; TAC, tacrolimus; MMF, mycophenolate mofetil; Cmax, concentration maximum; Cmin, concentration minimum; eGFR, estimated glomerular filtration rate; PRED, prednisone; OR, odds ratio; CI, confidence interval; Css, concentration stationary state; EVE, everolimus; SIR, sirolimus; BSX, basiliximab; ATG, anti-thymocyte globulin; C0, initial concentration; IQR, interquartile range; m, months; y, years; PK, pharmacokinetics; CL/F, apparent plasma clearance of drug after extravascular administration; V/F, apparent volume of distribution after extravascular administration; EBPR, endomyocardial biopsy-proven rejection; mTOR, mammalian target of rapamycin; RI, renal insufficiency; AE, adverse events; H, heart; R, renal; L, lung; vs., versus; ng, nanograms; mg, milligrams; mL, milliliters; MDRD, modification of diet in renal disease; RHC, rejection with hemodynamic compromise; CMV, citomegalovirus.

*3.3. Immunomodulatory Pathway*

- Cytokines and growth factors may play a significant role in modulating the immune response and triggering acute transplant rejection; therefore, controlling cytokine production represents a potential strategy to reduce the risk of rejection. Human Leukocyte Antigen G (HLA-G)

HLA-G is an immunomodulatory molecule that plays a crucial role in immune tolerance, particularly in the context of transplantation. In heart transplantation, HLA-G has been studied for its potential to promote graft acceptance and reduce the risk of rejection. HLA-G expression and function can be influenced by genetic polymorphisms, which may affect cardiac transplant tolerance and drug response (Table 3). The homozygous genotype HLA-G −14/−14bp (rs371194629) was associated with lower rejection, higher production of soluble HLA-G and better CSA absorption in a small Spanish cohort [48]. A large cohort of adult Canadian heart transplant recipients reported higher cell-mediated rejection development with variant allele of HLA-G +3196C/G (rs1610696), but no influence of the rest of HLA-G SNPs [49].

- Tumor Necrosis Factor alfa (TNF-$\alpha$)

TNF-$\alpha$ is implicated in the pathogenesis of acute and chronic allograft rejection by promoting inflammation, endothelial dysfunction, and the activation of various immune cells (such as T-cells and macrophages). The variant A allele TNF-$\alpha$ −308 G/A (rs1800629) was associated with higher TNF-$\alpha$ production, higher rejection, and higher mortality associated with acute rejection in cohort of United Kingdom [50] (Table 3). In the same line, the haplotypes of variant TNF-$\alpha$ (rs1800629) and TNF-ß (rs909253) alleles were associated with higher cardiac allograft vasculopathy and mortality [51]. However, TNF-$\alpha$ rs1800629 was not related to rejection in the previous study [51] and a large pediatric cohort [52], as well as no association with renal disfunction in another pediatric cohort [27].

- Transforming Growth Factor- ß1 (TGF-ß1)

TGF-ß1 is the most extensively investigated cytokine in the context of heart transplantation (Table 3), due to its role as a collagen inducer with profibrotic effects during the progression of glomerulonephritis resulting from CNI-induced nephrotoxicity. Polymorphisms located in the promoter region of the TGF-ß1 gene have been associated with decreased expression levels of this cytokine [53]. The variant alleles of two TGF-ß1 polymorphisms (rs1800470 and rs1800471) were associated with CNI-induced renal dysfunction post-transplantation in 3 large studies on cardiac transplant recipients [42,43,44], whereas other 4 studies did not obtain significant differences in renal function [26,37,46,49]. Furthermore, the variant allele C was associated with higher rejection endomyocardial biopsy-proven in patients ≥55 years during the first year after transplant [54]. On the other hand, the minor allele of rs4803455 TGF-ß1 polymorphism improved renal function in eGFR at 1 year after transplantation [36].

- Other cytokines and growth factors

Polymorphisms in cytokine genes and growth factors were analyzed in immunosuppressive treatment after heart transplantation. In a large, multiethnic cohort study involving 323 pediatric cardiac recipients found that acute rejection within five years was associated with a specific genetic profile: high-expression genotypes of VEGF (rs699947, rs833061, rs2010963), high-expression IL-6 (rs1800795), and low-expression IL-10 variants (rs1800896, rs1800871, rs1800872), but not with TNF-$\alpha$ (rs1800629) [52]. On the other hand, a cohort of 453 pediatric heart transplant recipients, variant alleles of IL-4 (rs2243250), IL-6 (rs1800795), IL-10 (rs1800896, rs1800871, rs1800872), IL-1RN (rs380092), IL15RA ( +21G > A, +5165T > A) were not correlated with CNI renal dysfunction [27].

The connective tissue growth factor (CTGF) expression has been shown to be up-regulated in in vitro models of chronic heart allograft rejection. Importantly, individuals carrying the C allele of the CTGF rs6918698 polymorphism have been linked to a heightened risk of developing cardiac allograft vasculopathy, a critical surrogate indicator of chronic rejection [55].

### *3.4. Other Genes*

The nucleotide-binding oligomerization domain-containing protein 2 (NOD2), also known as caspase recruitment domain-containing protein 15 (CARD15), plays a key role in the recognition of intracellular pathogens and the activation of lymphocytes. Two Spanish studies observed increased graft rejection with wild-type genotype of NOD2/CARD15 (rs2066844) [15]. A similar effect was reported with an angiotensin-converting enzyme (ACE) polymorphism (rs4646994), developing cardiac allograft vasculopathy at 6 years post-transplantation [56].

A Canadian study in 158 heart transplants analyzed 358 SNPs related to the renin–angiotensin–aldosterone system (RAAS), natriuretic peptides, and CNI nephrotoxicity, finding an association between post-transplant eGFR and a SNP in the protein kinase C-β gene (PRKCB; rs11074606), the gene implicated in RAAS intracellular signaling [57].

In a cohort of 115 cardiac transplant patients previously cited, the authors analyzed 184 variants of 34 genes with CNI nephrotoxicity [58]. They observed significant associations in European Americans (99 recipients) and in total population with polymorphisms of DPYD (rs1801265), UGT2B17 (rs1902023), SLCO1B1 (rs4149056), and SLC22A1 (rs34305973) genes, although most of them are genes related to MMF pathway. Similarly, in a cohort of 453 pediatric heart recipients treated with CNI, 19 functional SNPs in 14 candidate genes were analyzed, finding associations with renal dysfunction after cardiac transplantation and variant alleles of FASL (rs763110) and HO-1 (rs17879828) [27].

A genome-wide association study (GWAS) correlated improvements in eGFR with minor alleles of polymorphisms in LINC01121, BTBD7P2, MARCH1, ELAVL2, and HMHB1 genes in 251 patients after 1 year of heart transplantation [59]. Another GWAS performed on adult heart transplant recipients showed similar improvements in eGFR with variant alleles of HMHB1, LOC339894, LOC10042392, MMP12, and C12orf75 [60].

**Table 3.** Characteristics of the studies included in systematic review for immunomodulatory pathway and other genes.

| SNP | Study | n | Age Recipient (Range) | Age Donor (Range) | Ethnia Recipient | Ethnia Donor | HWE | Immunossupresant Scheme | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| **HLA-G** | | | | | | | | | |
| 14-bp indel rs371194629 | Torres 2009 [48] | 37 | 44 ± 12 | NR | NR (Spain) | NR (Spain) | Yes | CSA + MMF or EVE + CORT | ▪ Rejection: homozygous genotype −14/−14bp was associated with lower rejection, higher production of soluble HLA-G, and better CSA absorption. |
| | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences in CMR. |
| −201 G/A rs1233333 | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences in CMR. |
| −725C/G/T rs1233334 | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | No | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences in CMR. |
| +3196C/G rs1610696 | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: recipients with G allele associated with >CMR (univariable and multivariable analyses). |
| +3187A/G rs9380142 | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences in CMR. |
| +3142C/G rs1063320 | Adamson 2020 [49] | 123 | 48 ± 12 | 36 ± 14 | Caucasian 23% Black 2% Other 3% Unknown 72% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences in CMR. |
| **TNF-A** | | | | | | | | | Tumor necrosis factor-alpha |
| −308 G > A rs1800629 | Azzawi 2001 [50] | 119 | NR | NR | NR (United Kingdom) | NR (United | NR | CSA + AZA + CORT | ▪ Rejection: An allele was associated with higher TNF-A production, higher rejection, and higher |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Kingdom) | | | mortality associated with acute rejection. |
| | Ternstrom 2005 [51] | 70 | 48 ± 2 | 36 ± 2 | NR (Sweden) | NR (Sweden) | NR | CSA + AZA + CORT | ▪ CAV: haplotype of variant TNF-A and TNF-B was associated with higher CAV and mortality.<br>▪ Acute rejection: no differences. |
| | Girnita 2008 [52] | 323 | NR (Pediatric) | NR | White 63.5%<br>Black 13.3%<br>Hispanic 23.2% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: no differences. |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60%<br>Black 13%<br>Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **TNF-B** | | | | | | | | | |
| +252 G > A (rs909253) | Ternstrom 2005 [51] | 70 | 48 ± 2 | 36 ± 2 | NR (Sweden) | NR (Sweden) | NR | CSA + AZA + CORT | ▪ CAV: haplotype of variant TNF-A and TNF-B was associated with higher CAV and mortality.<br>▪ - Acute rejection: no differences. |
| **TGF-B1** | | | | | | | | | |
| 914 G > C (syn. Arg25 > Pro, codon 25) rs1800471 | Densem 1999 [61] | 121 | NR | NR | NR (United Kingdom) | NR (United Kingdom) | NR | CSA based schemes | ▪ Renal function (serum creatinine): no influence.<br>▪ CSA levels: no influence. |
| | Baan 2000 [53] | 168 | 44 ± 12 or 48 ± 9 (Cr < or > 250 μmol/L ) | NR | Caucasian 95%<br>Unknown 5% | NR | NR | CSA based schemes | ▪ Renal function: variant allele (Pro) was associated with renal dysfunction at 7 years post-transplantation. |
| | Lacha 2001 [62] | 298 | NR | NR | NR (Czech Republic) | NR (Czech Republic) | NR | CSA + AZA + CORT | ▪ Renal function: variant allele (Pro) and haplotype Pro10-Arg25 genotypes were associated with progression of renal insufficiency.<br>▪ CSA plasma trough levels: no differences. |
| | Wetering 2006 [63] | 402 | 50 (range: 4–71) | NR | NR (Netherlands) | NR (Netherlands) | NR | CSA/TAC + AZA/MMF + CORT | ▪ Renal function: variant allele C was associated with 2.6-fold higher risk of end-stage renal failure ($p = 0.002$) and higher time with dialysis ($p = 0.01$). |
| | Klauke 2008 [35] | 106 | RI (n = 53): 50.2 ± 14.6<br>noRI (n = 53): | RI (n = 53): 35.5 ± 13.7<br>noRI (n = 53): 34.2 ± 12.1 | NR | NR | NR | CSA/TAC + AZA/MMF + CORT ± imTOR | ▪ Renal function: no significant differences. |

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| | | | 51.3 ± 10.7 | | | | | | |
| | Benza 2009 [54] | 108 | 52 ± 11 | NR | African 14% Caucasian 86% | African 14% Caucasian 86% | NR | CSA + MMF + CORT | ▪ Rejection (endomyocardial biopsy-proven): variant allele C was associated with higher rejection rate in patients ≥55 years during the first year after transplant. |
| | Lachance2012 [57] | 158 | 53 (IQR: 43–58) | NR | Caucasian 98% Unknown 2% | NR (Canada) | NR | CSA/TAC + MMF/AZA + CORT | ▪ Renal function: no influence on eGFR post-transplantation.<br>▪ CNI levels: no influence. |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| 869 T > C (syn. Leu10> Pro, codon 10) rs1800470 | Baan 2000 [53] | 168 | 44 ± 12 or 48 ± 9 (Cr < or > 250 µmol/L ) | NR | Caucasian 95% Unknown 5% | NR | NR | CSA based schemes | ▪ Renal function: no influence. |
| | Lacha 2001 [62] | 298 | NR | NR | NR (Czech Republic) | NR (Czech Republic) | NR | CSA + AZA + CORT | ▪ Renal function: variant allele (Arg25) and haplotype Pro10-Arg25 genotypes were associated with progression in renal insufficiency.<br>▪ CSA plasma trough levels: no differences. |
| | Wetering 2006 [63] | 402 | 50 (range: 4–71) | NR | NR (Netherlands) | NR (Netherlands) | NR | CSA/TAC + AZA/MMF + CORT | ▪ Renal function: variant allele C was associated with 2.9-fold higher risk of end-stage renal failure ($p$ = 0.002) and higher time with dialysis ($p$ = 0.001). |
| | Klauke 2008 [35] | 106 | RI (n = 53): 50.2 ± 14.6 noRI (n = 53): 51.3 ± 10.7 | RI (n = 53): 35.5 ± 13.7 noRI (n = 53): 34.2 ± 12.1 | NR | NR | NR | CSA/TAC + AZA/MMF + CORT ± mTOR | ▪ Renal function: no significant differences. |
| | Lachance 2012 [57] | 158 | 53 (IQR: 43–58) | NR | Caucasian 98% Unknown 2% | NR (Canada) | NR | CSA/TAC + MMF/AZA + CORT | ▪ Renal function: no influence on eGFR post-transplantation.<br>▪ CNI levels: no influence. |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| rs4803455 C > A | Oreschak 2021 [37] | 192 | 49 ± 12 | NR | Caucasian 79% Black 9% Asian 4% | NR | Yes | TAC or CSA + MMF or AZA + CORT | Renal function: minor allele C improved renal function in eGFR at 1 year after transplantation (univariable and multivariable analyses). |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | Other 8% | | | | |
| **IL-4** | | | | | | | | | |
| −590 C > T rs2243250 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | No | CSA or TAC | ▪ Renal function: no significant differences. |
| **IL-6** | | | | | | | | | |
| −174 G/C rs1800795 | Girnita 2008 [52] | 323 | NR (Pediatric) | NR | White 63.5% Black 13.3% Hispanic 23.2% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: combination VEGF high/IL-6 high/ IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.0004) and marginally with repeat rejection ($p$ = 0.051).<br>▪ Rejection: combination IL-6 high/IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.020) and marginally with repeat rejection ($p$ = 0.015). |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | No | CSA or TAC | ▪ Renal function: no significant differences. |
| **IL-10** | | | | | | | | | |
| 1082 G/A 819 C/T 592 C/A | Girnita 2008 [52] | 323 | NR (Pediatric) | NR | White 63.5% Black 13.3% Hispanic 23.2% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: combination VEGF high/IL-6 high/ IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.0004) and marginally with repeat rejection ($p$ = 0.051).<br>▪ Rejection: combination IL-6 high/IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.020) and marginally with repeat rejection ($p$ = 0.015).<br>▪ Rejection: combination VEGF high/IL-6 high/ IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.021). |
| 1082 G/A | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **IL-1RN** | | | | | | | | | |
| VNTRs in intron 2 rs380092 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **IL15RA** | | | | | | | | | |
| +21G > A | Feingold 2012 | 453 | 6.2 ± 6.1 | NR | White 60% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |

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|---|---|---|---|---|---|---|---|---|---|
| | [27] | | | | Black 13%<br>Hispanic 23% | | | | |
| +5165T > A | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60%<br>Black 13%<br>Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **VEGF** | | | | | | | | | |
| 2578 C/A<br>460 C/T<br>405 C/G | Girnita 2008 [52] | 323 | NR (Pediatric) | NR | White 63.5%<br>Black 13.3%<br>Hispanic 23.2% | NR | Yes | TAC or CSA + MMF or AZA + CORT | ▪ Rejection: combination VEGF high/IL-6 high/ IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.0004) and marginally with repeat rejection ($p$ = 0.051).<br>▪ Rejection: combination VEGF high/IL-6 high/ IL-10 low was associated with increased estimated risk of late rejection ($p$ = 0.021). |
| **PRKCB** | | | | | | | | | |
| rs11074606 | Lachance 2012 [57] | 158 | 53 (IQR: 43–58) | NR | Caucasian 98%<br>Unknown 2% | NR (Canada) | NR | CSA/TAC + MMF/AZA + CORT | ▪ Renal function: predictor of post-transplant eGFR after adjusting for multiple comparisons ($p$ = 0.00049).<br>▪ CNI levels: no influence. |
| **NOD2/CARD15** | | | | | | | | | |
| rs2066844 C > T | Jordán 2012 [46] | 60 | NR | NR | NR | NR | NR | CSA or TAC | ▪ Rejection: CC significantly increase rejection ($p$ = 0.049). |
| | Sánchez-Lázaro 2015 [15] | 60 | CSA (n = 36): 53 ± 11<br>TAC (n = 24): 52 ± 10 | CSA (n = 36): 42 ± 12<br>TAC (n = 24): 43 ± 9 | NR | NR | NR | CSA or TAC + MMF + CORT | ▪ Rejection: a tendency of rejection at first year after transplantation for CC carriers compared with CT/TT carriers ($p$ = 0.050). |
| **LINC01121** | | | | | | | | | |
| rs17033285 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8%<br>American Indian 0.4%<br>Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele 17.3-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| rs76427116 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8%<br>American Indian 0.4%<br>Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele change in eGFR at 1 year after transplantation (improvement in renal function). |

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|---|---|---|---|---|---|---|---|---|---|
| **BTBD7P** | | | | | | | | | |
| rs4917601 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8% American Indian 0.4% Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele 11.6-fold change in eGFR at 1 year after transplantation (improvement in renal function). Similar effect with rs4617520, rs7095911, rs11195513, rs4465313, rs7923594, and rs4918638. |
| **MARCH** | | | | | | | | | |
| rs9762450 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8% American Indian 0.4% Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele 7.8–8.7-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **ELAVL2** | | | | | | | | | |
| rs12057071 rs13294337 rs1431304 rs2891188 rs7024224 rs10966079 rs10966081 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8% American Indian 0.4% Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele 12.1–13.2-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **HMHB1** | | | | | | | | | |
| rs918378 rs10463361 rs72795604 rs11167832 | Asleh 2018 [59] | 251 | 50.3 ± 13 | 32 ± 12 | Caucasian 96.8% American Indian 0.4% Unknown 2.8% | NR | NR | (CSA or TAC) or SIRO + MMF or AZA | Renal function: minor allele 13.6–14.2-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| rs918378 | Snipelisky 2017 [60] | 287 | NR | NR | NR (USA) | NR | NR | CNI | Renal function: minor allele 14.18-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **LOC339894** | | | | | | | | | |
| | Snipelisky 2017 [60] | 287 | NR | NR | NR (USA) | NR | NR | CNI | Renal function: minor allele 12.61-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **LOC10042392** | | | | | | | | | |
| rs4617520 | Snipelisky 2017 [60] | 287 | NR | NR | NR (USA) | NR | NR | CNI | Renal function: minor allele 11.95-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **MMP12** | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| rs652438 | Snipelisky 2017 [60] | 287 | NR | NR | NR (USA) | NR | NR | CNI | Renal function: minor allele 16.7-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **C12orf75** | | | | | | | | | |
| rs1230081 | Snipelisky 2017 [60] | 287 | NR | NR | NR (USA) | NR | NR | CNI | Renal function: minor allele 14.55-fold change in eGFR at 1 year after transplantation (improvement in renal function). |
| **PLCB1** | | | | | | | | | |
| rs170549 A > G | Oreschak 2021 [37] | 192 | 49 ± 12 | NR | Caucasian 79%<br>Black 9%<br>Asian 4%<br>Other 8% | NR | Yes | TAC or CSA + MMF or AZA + CORT | Renal function: minor allele A was associated with renal dysfunction in eGFR at 1 year after transplantation (univariable and multivariable analyses). |
| **ACE** | | | | | | | | | |
| Intron 16; Insertion (I); Deletion (D) rs4646994 | Pethig 2000 [56] | 146 | 46 ± 11 | NR | NR (Germany) | NR (Germany) | NR | CSA + AZA + CORT | ▪ CAV: DD genotype was associated with higher CAV than II and DI genotypes at 6 years post-transplant. |
| | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60%<br>Black 13%<br>Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **CTGF/CCN2** | | | | | | | | | |
| 945 C > G rs6918698 | Pantou 2012 [55] | 72 | 38 ± 14 (14–63) | NR | NR (Greece) | NR (Greece) | Yes | EVE + CNI + CORT | ▪ CAV: recipient CC genotype was associated with higher CAV. |
| G > A (rs13218743) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7%<br>African American 10.8%<br>Asian 4.1%<br>Other 7.4% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: associated with leukopenia in the first 12 months post-transplant, with variant carriers having higher odds compared to wild-type homozygotes ($p < 0.05$). |
| **HNF1A** | | | | | | | | | |
| A > C (p.I27L) (rs1169288) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7%<br>African American 10.8%<br>Asian 4.1%<br>Other 7.4% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: C allele carriers were significantly associated in the first six months post-transplant compared to A/A genotype ($p = 0.002$). Higher odds were observed in heterozygotes (OR 6.84; 95% CI: 2.11–22.12; $p = 0.001$) when compared to A/A patients.<br>▪ Association with leukopenia in the first 12 months post-transplant was also observed, |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | with variant carriers having higher odds compared to wild-type homozygotes ($p < 0.05$). |
| T > C (rs2393791) | Oreschak 2021 [37] | 148 | 49 ± 13 | NR | European American 77.7% African American 10.8% Asian 4.1% Other 7.4% | NR | NR | TAC/CSA ± MMF/AZA + CORT | ▪ MMF and/or CMV antiviral-induced leukopenia: Association with leukopenia in the first 12 months post-transplant, with variant carriers having higher odds compared to wild-type homozygotes ($p < 0.05$). |
| **HO-1** | | | | | | | | | |
| −489 A > T rs2071746 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| 326 A > G rs17879828 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | No | CSA or TAC | ▪ Renal function: the variant TT genotype was associated with decreased renal function (eGFR) after heart transplantation ($p = 0.004$) but this association was lost after multivariable analysis. |
| **NOS2** | | | | | | | | | |
| Ser608Leu rs2297518 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| +38 C > G rs10459953 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **FAS** | | | | | | | | | |
| −670 A > G rs71800682 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: no significant differences. |
| **FASL** | | | | | | | | | |
| −844 C > T rs763110 | Feingold 2012 [27] | 453 | 6.2 ± 6.1 | NR | White 60% Black 13% Hispanic 23% | NR | Yes | CSA or TAC | ▪ Renal function: the variant TT genotype was associated with decreased renal function (eGFR) after heart transplantation ($p = 0.033$) but this association was lost after multivariable analysis. |

Abbreviatures: SNP, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; HLA-G, human leukocyte antigen G; A, adenine; G, guanine; C, citosine; T, timine; U, uracil; NR, not reported; CSA, cyclosporine; MMF, mycophenolate mofetil; EVE, everolimus; CORT, corticosteroids; bp, base pairs; AZA, azathioprine; CMR, cell-mediated rejection; TNF-A, tumor necrosis factor-alpha; CAV, cardiac allograft vasculopathy; TNF-B, tumor necrosis factor beta; Cr,

creatinine; µmol, micromol; l, liters; eGFR, estimated glomerular filtration rate; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin; RI, renal insufficiency; IQR, interquartile range; TGFB1, transforming growth factor-ß1; IL, interleukin; VEGF, vascular endothelial growth factor; PRKCB, protein kinase C beta; NOD2, nucleotide-binding oligomerization domain containing 2; CARD15, caspase-activating recruitment domain 15; LINC01121, long intergenic non-protein-coding RNA 1121; SIR, sirolimus; BTBD7P, bric-a-brac/tramtrack/broad complex domain containing 7 pseudogene 2; MARCH1, membrane-associated ring-CH-type finger 1; ELAVL2, embryonic lethal abnormal vision-like RNA binding protein 2; HMHB1, histocompatibility minor HB-1; MMP12, matrix metalloproteinase-12; PLCB1, phospholipase C beta 1; ACE, angiotensin-converting enzyme; CTGF, connective tissue growth factor; CMV, citomegalovirus; HNF1A, hepatocyte nuclear factor 1 homeobox A; OR, odds ratio; CI, confidence interval; HO-1, heme oxygenase 1; NOS2, nitric oxide synthase 2; FAS, fas cell surface death receptor; FASL, fas cell surface death receptor ligand.

## 4. Discussion

This systematic review highlights the significant impact of pharmacogenetic variability on the pharmacokinetics, efficacy, and safety of immunosuppressive drugs in heart transplantation patients. The findings suggest that polymorphisms in genes encoding drug-metabolizing enzymes, transporters, and immune response mediators may contribute substantially to interindividual variability in drug response, thus influencing clinical outcomes.

The CYP3A5 genotype was confirmed as a crucial determinant of tacrolimus pharmacokinetics. Patients expressing the CYP3A5*1 allele required significantly higher tacrolimus doses to achieve target concentrations compared to non-expressers [6]. This finding aligns with previous evidence highlighting the role of CYP3A5 in tacrolimus metabolism [3]. Furthermore, combined CYP3A4 and CYP3A5 genotypes provided enhanced precision in dose prediction, supporting their implementation in clinical practice for optimal dosing strategies. Conversely, the impact of CYP3A4 variants alone was less consistent, reinforcing the primary role of CYP3A5 in tacrolimus metabolism [7].

Regarding cyclosporine, CYP3A5 genotype associations were also observed, albeit with less pronounced effects than those seen with tacrolimus. Notably, CYP3A5*1 carriers experienced better renal outcomes, suggesting a nephroprotective effect that warrants further investigation [11].

For MPA, polymorphisms in UGT genes exhibited moderate effects on plasma concentrations and adverse events. Variants in UGT2B7 were linked to gastrointestinal intolerance and anemia [20], while UGT1A7 and UGT3'UTR variants influenced adverse hematological events [17]. Despite this, no significant impact was identified for UGT1A9 variants in MPA pharmacokinetics, suggesting a gene-specific influence in this metabolic pathway [15].

IMPDH polymorphisms demonstrated associations with gastrointestinal toxicity and neutropenia in pediatric heart transplant recipients [20]. Although these findings highlight potential genetic predictors for adverse effects, their impact on immunosuppressive efficacy remains unclear and requires further investigation.

With regard to azathioprine, TPMT variants were confirmed as significant predictors of drug toxicity. Heterozygous carriers experienced lower enzyme activity, resulting in earlier and more severe adverse effects [21]. This supports the established recommendation for TPMT genotyping before initiating azathioprine therapy to mitigate toxicity risk.

Transporter gene polymorphisms were widely investigated with mixed results. ABCB1 variants were inconsistently associated with calcineurin inhibitor pharmacokinetics and nephrotoxicity. Some studies reported higher tacrolimus and cyclosporine concentrations in wild-type ABCB1 genotypes [2], while others found no association [11]. Additionally, ABCC2 variants showed potential links to gastrointestinal intolerance with MMF and improved graft survival outcomes in pediatric cohorts [43]. These discrepancies suggest that additional factors, such as sample size or ethnic variability, may influence transporter gene effects.

Cytokine and immune response gene polymorphisms also exhibited variable associations with clinical outcomes. Notable findings included the association of HLA-G variants with reduced acute rejection risk and improved CSA absorption [48]. Conversely, TNF-$\alpha$ polymorphisms correlated with higher mortality rates and acute rejection events in some studies [50]. Similarly, TGF-$\beta$1 variants were linked to calcineurin inhibitor-induced nephrotoxicity and graft rejection [53].

## 5. Conclusions

In conclusion, the findings underscore the relevance of pharmacogenetic testing in personalizing immunosuppressive therapy following heart transplantation. While strong evidence supports genotyping for CYP3A5 and TPMT to guide tacrolimus and azathioprine dosing, further research is required to validate the clinical utility of other genetic markers, particularly for transporter genes and cytokine polymorphisms. Implementing pharmacogenetic screening could enhance therapeutic outcomes by improving drug efficacy, reducing toxicity, and ultimately increasing graft survival rates in heart transplant recipients. We recommend pharmacogenetic testing for all patients undergoing heart transplantation. Ideally, testing should be integrated into the pre-transplant evaluation process to enable personalization of immunosuppressive therapy, or as early as possible post-transplant, before therapeutic drug levels are stabilized. The target genes that should be tested included the following: CYP3A5 (especially rs776746), in combination with CYP3A4 (rs2242480, rs35599367) and POR*28 (rs1057868), due to their impact on tacrolimus metabolism and dose requirements; TPMT (rs1142345, rs1800460, rs1800462) for azathioprine, associated with hematologic toxicity; UGT2B7 and ABCC2 for mycophenolate; and HLA-G (rs371194629), TNF-$\alpha$ (rs1800629), and TGF-$\beta$1 (rs1800470, rs1800471) for rejection risk and post-transplant renal function.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| CNI | Calcineurin inhibitor |
| MMF | Mycophenolate mofetil |
| mTOR | Mammalian target of rapamycin |
| DARE | Database of abstracts or reviews of effects |
| CYP | Cytochrome P450 |
| eGFR | Estimated glomerular filtration rate |
| POR | Cytochrome P450 oxidoreductase |
| NR1I2 | Nuclear Receptor Subfamily 1 Group I Member 2 |
| PXR | Pregnane X receptor |
| UGT | Uridine glycosyltransferase |
| MPA | Mycophenolic acid |
| IMPDH | Inosine monophosphate dehydrogenase |
| TPMT | Thiopurine methyltransferase |
| ABCB1 | ATP-binding cassette transporter B family member 1 |
| P-gp | P-glycoprotein |
| ABCB2 | ATP-binding cassette transporter B family member 2 |
| MRP2 | Multidrug resistance protein 2 |
| SLCO1B1 | Solute carrier organic anion transporter family member 1B1 |

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|---|---|
| SLC13A1 | Solute carrier family 13 member 1 |
| HLA-G | Human leukocyte antigen G |
| TNF-$\alpha$ | Tumor necrosis factor alfa |
| TGF-ß1 | Transforming growth factor- ß1 |
| CTGF | Connective tissue growth factor |
| NOD2 | Nucleotide-binding oligomerization domain containing 2 |
| CARD15 | Caspase-activating recruitment domain 15 |
| ACE | Angiostensin-converting enzyme |
| RAAS | Renin–angiotensin–aldosterone system |
| GWAS | Genome-wide association study |
| SNP | Single nucleotide polymorphisms |
| HWE | Hardy–Weinberg equilibrium |
| A | Adenine |
| G | Guanine |
| C | Citosine |
| T | Timine |
| U | Uracil |
| NR | Not reported |
| TAC | Tacrolimus |
| CORT | Corticosteroids |
| CL/F | Apparent plasma clearance of drug after extravascular administration |
| POD | Postoperative day |
| CL | Clearance |
| PRED | Prednisone |
| CSA | Cyclosporine |
| AZA | Azathioprine |
| SIR | Sirolimus |
| BSX | Basiliximab |
| ATG | Anti-thymocyte globulin |
| AUC | Area under the curve |
| Cmax | Concentration maximum |
| t max | Time maximum |
| Css | Concentration stationary state |
| USA | United States of America |
| C0/D | Initial concentration–dose relationship |
| TDD | Total daily dose |
| CI | Confidence interval |
| RI | Renal insufficiency |
| ng | Nanograms |
| ml | Milliliters |
| IQR | Interquartile range |
| min | Minutes |
| $m^2$ | Square meters |
| C0 | Initial concentration |
| m | Months |
| y | Years |
| mg | Milligrams |
| kg | Kilograms |

| | |
|---|---|
| d | Days |
| PK | Pharmacokinetics |
| EVE | Everolimus |
| V/F | Apparent volume of distribution after extravascular administration |
| L | Liters |
| h | Hours |
| vs. | Versus |
| AUC0–12 | Area under the curve from 0 to 12 h |
| $R^2$ | Coefficient of determination |
| Cmin | Concentration minimum |
| HTx | Heart transplantation |
| POR | Cytochrome P450 oxidoreductase |
| NR1I2 | Nuclear receptor subfamily 1 group I member 2 |
| PXR | Pregnane X receptor |
| UGT | Uridine glycosyltransferase |
| CMV | Citomegalovirus |
| AcMPAG | Acyl glucuronide of mycophenolic acid |
| IMPDH | Inosine monophosphate dehydrogenase |
| TPMT | Thiopurine methyltransferase |
| HZ | Heterozygous |
| WT | Wild type |
| ABCB1 | ATP-binding cassette transporter B family member 1 |
| AUC0–4 | Area under the curve from 0 to 4 h |
| OR | Odds ratio |
| V/F | Apparent volume of distribution after extravascular administration |
| EBPR | Endomyocardial biopsy-proven rejection |
| AE | Adverse events |
| MDRD | Modification of diet in renal disease |
| RHC | Rejection with hemodynamic compromise |
| bp | Base pairs |
| CMR | Cell-mediated rejection |
| CAV | Cardiac allograft vasculopathy |
| TNF-B | Tumor necrosis factor beta |
| Cr | Creatinine |
| μmol | Micromol |
| IL | Interleukin |
| VEGF | Vascular endothelial growth factor |
| PRKCB | Protein kinase C beta |
| LINC01121 | Long intergenic non-protein coding RNA 1121 |
| BTBD7P | Bric-a-brac/tramtrack/broad complex domain containing 7 pseudogene 2 |
| MARCH1 | Membrane-associated ring-CH-type finger 1 |
| ELAVL2 | Embryonic lethal abnormal vision-like RNA binding protein 2 |
| HMHB1 | Histocompatibility minor HB-1 |
| MMP12 | Matrix metalloproteinase-12 |
| PLCB1 | Phospholipase C beta 1 |
| CTGF | Connective tissue growth factor |
| HNF1A | Hepatocyte nuclear factor 1 homeobox A |
| HO-1 | Heme oxygenase 1 |

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|---|---|
| NOS2 | Nitric oxide synthase 2 |
| FAS | Fas cell surface death receptor |
| FASL | Fas cell surface death receptor ligand |

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