A Systematic Review and Meta-Analysis of Pharmacogenetic Studies in Patients with Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is an important global public health problem due to its high prevalence and morbidity. Although the treatment of nephrology patients has changed considerably, ineffectiveness and side effects of medications represent a major issue. In an effort to elucidate the contribution of genetic variants located in several genes in the response to treatment of patients with CKD, we performed a systematic review and meta-analysis of all available pharmacogenetics studies. The association between genotype distribution and response to medication was examined using the dominant, recessive, and additive inheritance models. Subgroup analysis based on ethnicity was also performed. In total, 29 studies were included in the meta-analysis, which examined the association of 11 genes (16 polymorphisms) with the response to treatment regarding CKD. Among the 29 studies, 18 studies included patients with renal transplantation, 8 involved patients with nephrotic syndrome, and 3 studies included patients with lupus nephritis. The present meta-analysis provides strong evidence for the contribution of variants harbored in the ABCB1, IL-10, ITPA, MIF, and TNF genes that creates some genetic predisposition that reduces effectiveness or is associated with adverse events of medications used in CKD.

Keywords: genetic association; chronic kidney disease; meta-analysis; pharmacogenetics; systematic review

1. Introduction

Chronic kidney disease (CKD) continues to constitute a global health burden. It is known that CKD elevates the risk of cardiovascular disease, kidney failure, and other complications [1–3]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification, CKD is defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m² for 3 months or more, irrespective of the cause [4]. Although significant progress has been made in the treatment of nephrology patients with both conservative therapies and dialysis or transplantation, the emergence of drug-related problems such as ineffectiveness and side effects represents a major issue [5]. Pharmacogenetics could fill this gap [6].

Over the last 30 years, new drugs have been introduced to treat major kidney diseases, slow down the progression of CKD, and reduce the development of clinical complications associated with dialysis and kidney transplantation [7]. The use of different combinations of potent immunosuppressive drugs in transplant patients (calcineurin inhibitors, mammalian
target of rapamycin inhibitors (mTORs), corticosteroids) have significantly improved the treatment of various renal disorders, and the short- and long-term pharmacological management of renal graft recipients [8].

In general, currently approved immunosuppressive drugs for maintenance therapy include calcineurin inhibitors (cyclosporine (CsA), tacrolimus (TAC)), mTOR inhibitors (sirolimus (SIR), everolimus), antiproliferatives (azathioprine (AZA) and mycophenolic acid (MPA)) and biologic drugs (belatacept) [9]. Differences between individuals regarding the efficacy and safety of immunosuppressive treatment are determined to some extent by genetic factors. For example, a common nonfunctional splicing variant, CYP3A5*3 (rs776746), determines TAC doses [10]. More specifically, patients with the CYP3A5*3/*3 genotype require less TAC to reach target concentrations compared with cytochrome P450 family 3 subfamily A member 5 (CYP3A5) CYP3A5*1 allele carriers [11]. Tacrolimus pharmacokinetic and pharmacodynamic variability is also attributed to ATP binding cassette subfamily B member 1 (ABCB1) variants: 1236C > T (rs1128503), 2677G > T/A (rs2032582), and 3435C > T (rs1045642) [12,13]. In addition, another example of the implication of pharmacogenetics in nephrology constitutes the thiopurine S-methyltransferase (TPMT) gene [14]. Many lines of evidence have reported that genetic variants located in the TPMT gene affect AZA metabolism and patients with low activity (10% prevalence) or absent activity (0.3% prevalence) are at risk of myelosuppression [15,16]. Among 20 variant alleles (TPMT *2-*18) identified to date, mutant alleles TPMT*2 and TPMT*3 explain more than 95% of defective gene activity [8,17].

“Adjusting” the dose of such drugs to the specific requirements of each patient to minimize toxicity while maintaining efficacy is a challenge in clinical nephrology. In an effort to provide the most comprehensive overview regarding the genetic contribution of pharmacogenes to the response to treatment of nephropathy patients, we performed a systematic review and meta-analysis of available pharmacogenetic studies that included patients with CKD regardless of the primary cause of the disease.

2. Results

A systematic review of the literature in the PubMed database identified 492 articles. After extensive study, 29 articles were included in the meta-analysis. Figure 1 shows the reasons for excluding articles. In total, 11 genes (ABCB1, CYP2C9, CYP2C19, CYP3A5, IL-6, IL-10, ITPA, MIF, TGFB1, TNF, TPMT) and 16 polymorphisms located in these genes were studied.

The characteristics of each study are listed in Table 1. The studies were conducted in various populations of different racial descent: 11 studies involved Caucasians, 14 studies recruited Asians, and 4 studies were conducted in ethnically mixed populations. Among the 29 studies, 18 studies included patients with renal transplantation, 8 recruited patients with nephrotic syndrome, and 3 studies included patients with lupus nephritis.
Figure 1. Flowchart of retrieved studies with reasons for exclusion.

The characteristics of each study are listed in Table 1. The studies were conducted in various populations of different racial descent: 11 studies involved Caucasians, 14 studies recruited Asians, and 4 studies were conducted in ethnically mixed populations. Among the 29 studies, 18 studies included patients with renal transplantation, 8 recruited patients with nephrotic syndrome, and 3 studies included patients with lupus nephritis.
Table 1. Demographic characteristics of included studies.

| Author (Year of Publication) | Ethnicity | Drug | Phenotype or Trait | Gene | Polymorphism (Rs Number) | N  | Selection Criteria of Non-Responders | Responders | N  | Selection Criteria of Responders |
|------------------------------|-----------|------|--------------------|------|--------------------------|----|-------------------------------------|------------|----|----------------------------------|
| Xiong, 2010 [18]             | East Asians | AZA  | Kidney transplant recipients | ITPA | 94C > A (rs1127354) | 35 | Hematotoxicity and/or hepatotoxicity and/or GI toxicity and/or flu-like symptoms Renal transplants, AZA treatment present or previously | 120 | No adverse drug reactions |
| Kurzawski, 2009 [19]         | Caucasians | AZA  | Renal transplant recipients | TPMT | *1 vs. *2,*3A,*3C 94C > A (rs1127354) | 108 | Leucopenia and/or Hepatotoxicity Renal transplants, AZA treatment previously | 48 | No adverse drug reactions |
| Wang, 2008 [20]              | Caucasians | TAC, MMF, PRE | Kidney transplant recipients (no antiviral, anticancer, or other leucopenia-causing medication) | IMPDH1 | 898G > A n2288550 1552G > A | 60 | Leucopenia Renal transplants | 129 | No adverse drug reactions |
| Xin, 2009 [21]               | East Asians | AZA, CsA, PRE | Renal transplant recipients | TPMT | *1 vs. *3C | 30 | Hematotoxicity and/or hepatotoxicity Renal transplants | 120 | No adverse drug reactions |
| Vannaprasaht, 2009 [22]      | Asians     | AZA, PRE, CNIs | Kidney transplant recipients | TPMT | *1 vs. *3C | 22 | Myelosuppression Renal transplants | 117 | No adverse drug reactions |
| Takada, 2004 [23]            | Caucasians | pulse cyclophosphamide | Lupus nephritis | CYP2C19 | CYP2C19*2 (rs4244285) CYP2C9*2 (rs1799653) CYP3A5*3 (rs776746) | 28 | Development of premature ovarian failure Patients with lupus nephritis | 20 | No adverse drug reactions |
| Ngamjanyaporn, 2011 [24]     | Asians     | cyclophosphamide | SLE | CYP2C19 | *1 vs. *2 (rs4244285) | 36 | Ovarian toxicity Patients with systemic lupus erythematosus | 35 | No adverse drug reactions |
| Chiou, 2012 [25]             | Asians     | PRE  | Idiopathic NS | CYP3A5 | 6986A > G (rs5776746) C1236T (rs1128503) G2677T (rs2032582) G2677A (rs2032582) C3435T (rs1045642) | 16 | Steroid resistant NS Patients with NS | 58 | Steroid sensitive NS |
| Author (Year of Publication) | Ethnicity | Drug | Phenotype or Trait | Gene | Polymorphism (Rs Number) | N   | Selection Criteria of Non-Responders | Responders | N   | Selection Criteria of Responders |
|-----------------------------|-----------|------|-------------------|------|--------------------------|-----|-------------------------------------|------------|-----|----------------------------------|
| Youssef, 2013 [26]          | Mixed     | PRE  | Idiopathic NS     | ABCB1| C1236T (rs1128503)       | 46  | Steroid non-responders Patients with INS | 92         | Steroid responders                |
|                            |           |      |                   | ABCB1| G2677T/A (rs2032582)     |     |                                     |            |                               |
|                            |           |      |                   | ABCB1| C3435T (rs1045642)       |     |                                     |            |                               |
| Sadeghi-Bojd, 2019 [27]     | Asians    | steroids | Idiopathic NS    | MIF  | -173G > C (rs755622)     | 27  | Steroid resistant Patients with NS  | 107        | Steroid responders                |
| Luo, 2013 [28]              | East Asians | CsA | Gingival overgrowth in renal transplant recipients | IL-10 | -1082A > G -819C > T -592C > A | 122 | With gingival overgrowth Renal transplants | 80         | Without gingival overgrowth       |
|                            |           |      |                   | ABCB1| 1236C > T (rs1128503)    |     |                                     |            |                               |
|                            |           |      |                   | ABCB1| 2677G > T (rs2032582)    |     |                                     |            |                               |
|                            |           |      |                   | ABCB1| 2677G > A (rs2032582)    |     |                                     |            |                               |
|                            |           |      |                   | ABCB1| 3435C > T (rs1045642)    |     |                                     |            |                               |
| Choi, 2011 [29]             | East Asians | steroids | Idiopathic NS    | MIF  | G-173C (rs755622)        | 69  | Steroid non-responders Patients with NS | 101        | Steroid responders                |
| Berdeli, 2005 [30]          | Mixed     | steroids | Idiopathic NS    | MIF  | G-173C (rs755622)        | 77  | Steroid non-responders Patients with NS | 137        | Steroid responders                |
| Swierczewska, 2014 [31]     | Caucasians | steroids | Idiopathic NS    | MIF  | G-173C (rs755622)        | 41  | Steroid non-responders Patients with NS | 30         | Steroid responders                |
| Babel, 2004 [32]            | Caucasians | CsA+ TAC/PRE and ATG/anti-IL-2R antibody | Long-term renal transplants | IL10  | A-1082G (rs1800896)       | 51  | Type 2/steroid-induced DM Renal transplants | 207        | No adverse drug reactions        |
|                            |           |      |                   | TNFa | A-308G (rs1800032)       |     |                                     |            |                               |
|                            |           |      |                   | IL-6 | C-174G                   |     |                                     |            |                               |
|                            |           |      |                   | TGFBI10| C > T                   |     |                                     |            |                               |
| Author (Year of Publication) | Ethnicity       | Drug          | Phenotype or Trait                        | Gene   | Polymorphism (Rs Number) | N     | Selection Criteria of Non-Responders | Responders | N     | Selection Criteria of Responders |
|-----------------------------|----------------|---------------|-------------------------------------------|--------|--------------------------|-------|-------------------------------------|------------|-------|----------------------------------|
| Singh, 2011 [33]            | Asians         | CsA           | Rejection episodes in renal transplant recipients | ABCB1  | 1236 C > T (rs1128503)   | 49    | Rejection episodes                  | Renal transplants | 176   | No rejection episodes            |
|                             |                | CsA           |                                            | ABCB1  | 2677 G > T (rs2032582)   | 72    | Rejection episodes                  | Renal transplants | 176   | No rejection episodes            |
|                             |                | CsA           |                                            | ABCB1  | 3435 C > T (rs1045642)   | 70    | Rejection episodes                  | Renal transplants | 176   | No rejection episodes            |
|                             |                | CsA           |                                            | ABCB1  | 1236 C > T (rs1128503)   | 46    | Rejection episodes                  | Renal transplants | 29    | No rejection episodes            |
|                             |                | TAC           |                                            | ABCB1  | 2677 G > T (rs2032582)   | 46    | Rejection episodes                  | Renal transplants | 29    | No rejection episodes            |
|                             |                | TAC           |                                            | ABCB1  | 3435 C > T (rs1045642)   |       |                                     |             |       |                                  |
| Santoro, 2011 [34]          | Mixed          | CsA and AZA/SRL or TAC and AZA/SRL | Renal transplant patients | CYP3A5 | CYP3A5*3 (rs776746)       | 15    | Biopsy-proven rejection episodes    | Renal transplants | 138   | No biopsy-proven rejection episodes |
|                             |                | CsA           |                                            | ABCB1  | 1236 C > T (rs1128503)   | 139   | Biopsy-proven rejection episodes    | Renal transplants | 15    | No biopsy-proven rejection episodes |
|                             |                | TAC           |                                            | ABCB1  | 2677 G > T (rs2032582)   | 129   | Biopsy-proven rejection episodes    | Renal transplants | 15    | No biopsy-proven rejection episodes |
|                             |                | TAC           |                                            | ABCB1  | 3435 C > T (rs1045642)   | 140   | Biopsy-proven rejection episodes    | Renal transplants | 15    | No biopsy-proven rejection episodes |
| Glowacki, 2011 [35]         | Caucasians     | TAC           | Acute tubular necrosis/TAC tubular or vascular toxicity after renal transplantation | ABCB1  | 3435 C > T (rs1045642)   | 16    | Acute tubular necrosis/TAC tubular or vascular toxicity | Renal transplants | 187   | No acute tubular necrosis/TAC tubular or vascular toxicity |
| Kuypers, 2010 [36]          | Caucasians     | calcineurin inhibitor | Calcineurin inhibitor-associated nephrotoxicity in renal allograft recipients | CYP3A5 | CYP3A5*3 (rs776746)       | 51    | Calcineurin inhibitor-associated nephrotoxicity | Renal allograft recipients | 253   |                                  |
| Miura, 2008 [37]            | East Asians    | PRE and TAC and MMF | Acute rejection in renal transplant recipients | ABCB1  | 1236 C > T (rs1128503)   | 43    | Acute rejection                      | Renal transplants | 52    | No acute rejection               |
| Author (Year of Publication) | Ethnicity | Drug | Phenotype or Trait | Gene | Polymorphism (Rs Number) | N | Selection Criteria of Non-Responders | Responders | N | Selection Criteria of Responders |
|----------------------------|----------|------|-------------------|------|--------------------------|---|-------------------------------------|------------|---|-------------------------------|
| Grinyo, 2008 [38]          | Caucasians | CsA and MMF | Acute rejection after kidney transplantation | ABCB1 | 3435 C > T (rs1045642) 1236 C > T (rs1128503) 2677 G > T (rs2032582) 2677 G > A (rs2032582) | 77 | Biopsy-proven acute rejection | Renal transplants | 160 | No biopsy-proven acute rejection |
| Von Ahsen, 2001 [39]       | Caucasians | CsA | Rejection episodes in stable renal transplant recipients | ABCB1 | 3435 C > T (rs1045642) | 47 | Rejection | Renal transplants | 77 | No rejection |
| Quteineh, 2008 [40]        | Caucasians | TAC | Delayed allograft function in renal graft recipients | CYP3A5 | CYP3A5*3 (rs776746) | 77 | Delayed graft function | Renal transplants | 59 | No delayed graft function |
| Qiu, 2008 [41]             | East Asians | CsA | Rejection episodes in renal transplant recipients | ABCB1 | 1236 C > T (rs1128503) 2677 G > T/A (rs2032582) 3435 C > T (rs1045642) | 6 | Rejection | Renal transplants | 97 | No rejection |
| Kagaya, 2010 [42]          | Asians | MMF | Subclinical acute rejection after renal transplantation | IMPDH | rs2278293 | 21 | Subclinical acute rejection | Renal transplants | 61 | No subclinical acute rejection |
| Kurzawski, 2005 [43]       | Caucasians | AZA | AZA-induced myelotoxicity in renal transplant recipients | TPMT | *1 vs. *2,*3A,*3C | 67 | AZA-induced myelotoxicity | Renal transplants | 113 | No adverse drug reactions |
| Author (Year of Publication) | Ethnicity | Drug | Phenotype or Trait | Gene | Polymorphism (Rs Number) | N   | Selection Criteria of Non-Responders | Responders | N   | Selection Criteria of Responders |
|-----------------------------|-----------|------|-------------------|------|--------------------------|-----|-------------------------------------|------------|-----|----------------------------------|
| Kumaraswami, 2017 [44]     | Asians    | cyclophosphamide | Lupus nephritis | CYP2C19 | CYP2C19*2 (rs4244285)     | 24  | No response                        | Lupus nephritis patients | 123 | Complete and partial response    |
|                            |           |      |                   | CYP2C9 | CYP2C9*2 (rs1799853)     |     |                                     |                         |     |                                  |
|                            |           |      |                   | CYP3A5 | CYP3A5*3 (rs776746)      |     |                                     |                         |     |                                  |
| Moussa, 2017 [45]          | Mixed     | steroids | Pediatric idiopathic nephrotic syndrome | ABCB1 | C1236T (rs1128503) C2677A (rs1045642) C3435T (rs776746) | 10  | Steroid non-responders             | Idiopathic nephrotic syndrome | 53  | Steroid responders                |
| Tripathi, 2008 [46]        | Asians    | glucocorticoids | Idiopathic nephrotic syndrome | TNF-α A-308G (rs1800629) IL-6 G174C (rs1800795) | 35  | Steroid resistant                  | Idiopathic nephrotic syndrome | 115 | Steroid sensitive                |
In total, 16 genetic polymorphisms were examined in two or more studies and, therefore, were meta-analyzed. Tables 2–7 list the results of the meta-analyses that are indicative of the association of the respective polymorphism with the risk of side effects or non-response to medication in patients with CKD after calculating the odds ratio (OR) per genetic model.

Table 2. Meta-analysis results regarding pulse cyclophosphamide.

| Drug                      | Gene            | Polymorphism | Rs Number  | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I^2 (%) | p-Value for Q | p-Value for Egger Test | p-Value Begg–Mazumdar |
|---------------------------|-----------------|--------------|------------|--------------|------------------------------|------------------------------|---------|---------------|--------------------------|------------------------|
| Pulse cyclophosphamide All | CYP2C9          | CYP2C9*2     | rs1799853  | 2            | 1.24 (0.20–7.90)             | 1.24 (0.20–7.90)             | 0       | 0.41          | -                        | -                      |
| Dominant                  |                 |              |            |              | 1.89 (0.11–32.69)            | 1.89 (0.11–32.69)            | 0       | 0.52          | -                        | -                      |
| Recessive                 |                 |              |            |              | 1.93 (0.11–33.45)            | 1.93 (0.11–33.45)            | 0       | 0.54          | -                        | -                      |
| Additive                  |                 |              |            |              |                              |                              |         |               |                          |                        |
| Pulse cyclophosphamide All | CYP2C19         | CYP2C19*2    | rs4244285  | 3            | 1.07 (0.60–1.90)             | 0.81 (0.17–3.90)             | 86      | 0.001         | -                        | -                      |
| Dominant                  |                 |              |            |              | 1.25 (0.34–4.63)             | 1.25 (0.34–4.63)             | 0       | 0.89          | -                        | -                      |
| Recessive                 |                 |              |            |              | 1.36 (0.34–5.36)             | 1.36 (0.34–5.36)             | 0       | 0.48          | -                        | -                      |
| Additive                  |                 |              |            |              |                              |                              |         |               |                          |                        |
| Caucasians                |                 |              |            |              |                              |                              |         |               |                          |                        |
| Dominant                  |                 |              |            |              | 1.88 (0.98–3.60)             | 1.88 (0.98–3.60)             | 0       | 0.50          | -                        | -                      |
| Recessive                 |                 |              |            |              | 1.46 (0.33–3.67)             | 1.46 (0.33–3.67)             | 0       | 0.84          | -                        | -                      |
| Additive                  |                 |              |            |              | 2.06 (0.44–9.58)             | 2.06 (0.44–9.58)             | 0       | 0.94          | -                        | -                      |

Table 3. Meta-analysis results regarding prednisolone.

| Drug        | Gene       | Polymorphism | Rs Number  | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I^2 (%) | p-Value for Q | p-Value for Egger Test | p-Value Begg–Mazumdar |
|-------------|------------|--------------|------------|--------------|------------------------------|------------------------------|---------|---------------|--------------------------|------------------------|
| Prednisolone | TPMT       | *1 vs. *3C   | rs1045642  | 9            | 0.86 (0.63–1.18)             | 0.86 (0.63–1.18)             | 0%      | 0.61          | 0.62                      | 0.48                   |
| Dominant    | CYP3A5     | CYP3A5*3     | rs776746   | 2            | 2.38 (0.41–13.67)            | 2.38 (0.41–13.67)            | 0%      | 0.84          | -                        | -                      |
| Recessive   |            |              |            |              | 2.54 (1.03–6.22)             | 2.54 (1.03–6.22)             | 0%      | 0.73          | -                        | -                      |
| Additive    | ABCC1      | C3435T      | rs1045642  | 9            | 3.24 (0.54–19.51)            | 3.24 (0.54–19.51)            | 0%      | 0.80          | -                        | -                      |
| Dominant    |            |              |            |              | 0.86 (0.63–1.18)             | 0.86 (0.63–1.18)             | 0%      | 0.61          | 0.62                      | 0.48                   |
| Recessive   |            |              |            |              | 1.21 (0.86–1.70)             | 1.21 (0.86–1.70)             | 0%      | 0.76          | 0.72                      | 0.76                   |
| Additive    |            |              |            |              | 0.97 (0.64–1.48)             | 0.97 (0.64–1.48)             | 0%      | 0.95          | 0.31                      | 0.61                   |
| Drug       | Gene  | Polymorphism | Rs Number | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I² (%) | p-Value for Q | Egger Test p-Value | Begg–Mazumdar p-Value |
|------------|-------|--------------|-----------|--------------|-----------------------------|-----------------------------|--------|--------------|-------------------|---------------------|
|            |       |              |           |              |                             |                             |        |              |                   |                     |
|            |       |              |           |              |                             |                             |        |              |                   |                     |
| Caucasians |       |              |           |              |                             |                             |        |              |                   |                     |
| Dominant   | ABCB1 | C3435T       | rs1045642 | 2            | 1.02 (0.26–3.68)            | 1.05 (0.26–4.28)            | 14.7%  | 0.28         | -                 | -                   |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Asians     | ABCB1 | C3435T       | rs1045642 | 5            | 1.01 (0.62–1.51)            | 1.07 (0.66–1.75)            | 0%     | 0.99         | 0.79              | 0.82                |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Mixed      | ABCB1 | C3435T       | rs1045642 | 2            | 2.02 (0.82–4.96)            | 2.05 (0.73–5.75)            | 23.6%  | 0.25         | -                 | -                   |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| All        | ABCB1 | C1236T       | rs1128503 | 9            | 1.29 (0.91–1.84)            | 1.31 (0.90–1.89)            | 5%     | 0.39         | 0.62              | 0.36                |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Caucasians | ABCB1 | C1236T       | rs1128503 | 2            | 0.57 (0.39–1.44)            | 0.66 (0.19–2.31)            | 70.6%  | 0.07         | -                 | -                   |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Asians     | ABCB1 | C1236T       | rs1128503 | 5            | 1.17 (0.68–2.02)            | 1.17 (0.68–2.02)            | 0%     | 0.36         | -                 | -                   |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Mixed      | ABCB1 | C1236T       | rs1128503 | 2            | 0.76 (0.37–1.59)            | 0.76 (0.36–1.61)            | 3.8%   | 0.31         | -                 | -                   |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Prednizolone |       |              |           |              |                             |                             |        |              |                   |                     |
| Dominant   | ABCB1 | G2677T       | rs2032582 | 5            | 1.08 (0.60–1.93)            | 1.08 (0.60–1.93)            | 0%     | 0.83         | 0.43              | 0.23                |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Caucasians | ABCB1 | G2677T       | rs2032582 | 2            | 1.16 (0.67–2.01)            | 1.11 (0.48–2.57)            | 53.8%  | 0.07         | 0.72              | 0.08                |
| Dominant   |       |              |           |              |                             |                             |        |              |                   |                     |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |
| Prednizolone |       |              |           |              |                             |                             |        |              |                   |                     |
| Dominant   | ABCB1 | G2677A       | rs2032582 | 5            | 1.21 (0.62–2.37)            | 1.30 (0.59–2.84)            | 21.1%  | 0.28         | 0.16              | 0.08                |
| Recessive  |       |              |           |              |                             |                             |        |              |                   |                     |
| Additive   |       |              |           |              |                             |                             |        |              |                   |                     |

**Table 3. Cont.**
### Table 3. Cont.

| Drug       | Gene | Polymorphism Rs Number | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I² (%) | p-Value for Q | Egger Test p-Value | Begg–Mazumdar p-Value |
|------------|------|------------------------|-------------|------------------------------|------------------------------|--------|--------------|-------------------|----------------------|
| Prednisolone | MIF  | −173 G > C rs755622    | 4           |                              |                              |        |              |                   |                      |
| Dominant   | 1.56 | (1.09–2.24)            | 1.28        | 80.6%                        | 0.001                        | 0.16   | <0.0001      |                   |                      |
| Recessive  | 2.90 | (1.02–8.30)            | 2.88        | 45.3%                        | 0.14                         | 0.91   | 0.75         |                   |                      |
| Additive   | 2.98 | (1.03–8.63)            | 2.93        | 59.4%                        | 0.06                         | 0.92   | 0.75         |                   |                      |
| Prednisolone | IL-6 | C-174G rs1800795      | 2           |                              |                              |        |              |                   |                      |
| Dominant   | 0.82 | (0.49–1.37)            | 0.82        | 0%                           | 0.69                         | -      | -            |                   |                      |
| Recessive  | 0.80 | (0.43–1.48)            | 0.32        | 82.8%                        | 0.02                         | -      | -            |                   |                      |
| Additive   | 0.66 | (0.31–1.40)            | 0.31        | 80.9%                        | 0.02                         | -      | -            |                   |                      |
| Prednisolone | TNF  | G-308A                 | 2           |                              |                              |        |              |                   |                      |
| Dominant   | 0.82 | (0.49–1.38)            | 0.82        | 0%                           | 0.35                         | -      | -            |                   |                      |
| Recessive  | 0.12 | (0.02–0.65)            | 0.12        | 0%                           | 0.38                         | -      | -            |                   |                      |
| Additive   | 0.12 | (0.02–0.64)            | 0.12        | 0%                           | 0.38                         | -      | -            |                   |                      |

### Table 4. Meta-analysis results regarding MMF.

| Drug       | Gene | Polymorphism Rs Number | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I² (%) | p-Value for Q | Egger Test p-Value | Begg–Mazumdar p-Value |
|------------|------|------------------------|-------------|------------------------------|------------------------------|--------|--------------|-------------------|----------------------|
| MMF All    | ABCB1| 3435C > T rs1045642    | 2           | 2.07                         | (1.09–3.94)                  |        | 0.41         |                   |                      |
| Dominant   | 2.07 | (1.09–3.94)            | 2.07        | 0%                           | 0.41                         | -      | -            |                   |                      |
| Recessive  | 1.43 | (0.81–2.54)            | 1.27        | 46.3%                        | 0.17                         | -      | -            |                   |                      |
| Additive   | 2.25 | (1.05–4.84)            | 1.99        | 47.2%                        | 0.17                         | -      | -            |                   |                      |
| Prednisolone | ABCB1| 1236C > T rs1128503    | 2           |                              |                              |        |              |                   |                      |
| Dominant   | 1.67 | (0.93–3.00)            | 1.67        | 0%                           | 0.51                         | -      | -            |                   |                      |
| Recessive  | 1.89 | (1.05–3.40)            | 1.63        | 70.2%                        | 0.07                         | -      | -            |                   |                      |
| Additive   | 2.43 | (1.17–5.04)            | 2.13        | 33.9%                        | 0.22                         | -      | -            |                   |                      |
| Prednisolone | ABCB1| 2677G > T rs2002582    | 2           |                              |                              |        |              |                   |                      |
| Dominant   | 2.20 | (1.16–4.17)            | 2.20        | 0%                           | 0.81                         | -      | -            |                   |                      |
| MMF All    | ABCB1| 2677G > A rs2002582    | 2           |                              |                              |        |              |                   |                      |
| Dominant   | 3.72 | (0.72–19.22)           | 3.72        | 0%                           | 0.50                         | -      | -            |                   |                      |
| Recessive  | 3.04 | (0.22–42.65)           | 3.04        | 0%                           | 0.75                         | -      | -            |                   |                      |
| Additive   | 4.14 | (0.28–61.96)           | 4.14        | 0%                           | 0.94                         | -      | -            |                   |                      |
Table 5. Meta-analysis results regarding cyclosporine.

| Drug                  | Gene   | Polymorphism            | Rs Number | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I² (%) | p-Value for Q | Egger Test p-Value | Begg–Mazumdar p-Value |
|-----------------------|--------|-------------------------|-----------|--------------|-------------------------------|-------------------------------|--------|---------------|-------------------|---------------------|
| Cyclosporine (CsA) All | TPMT   | 1 vs. 3C                | 2         |              | 0.49 (0.18–1.37)             | 0.64 (0.01–50.02)             | 94.4%  | <0.0001       | -                 | -                   |
| Dominant              |        |                         |           |              |                               |                               |        |               |                   |                     |
| Recessive             | 1      |                         | 4         |              | (0.08–202.85)                | (0.08–202.85)                 | 0%     | >0.9999       | -                 | -                   |
| Additive              | 4.5    |                         | 4.5       |              | (0.09–228.51)                | (0.09–228.51)                 | 0%     | >0.9999       | -                 | -                   |
| CsA All               | IL10   | −1082A > G              | 3         |              |                               |                               |        |               |                   |                     |
| Dominant              |        |                         |           |              | 0.75 (0.49–1.14)             | 0.76 (0.42–1.37)              | 48.1%  | 0.15          | -                 | -                   |
| Recessive             | 1.11   |                         | 1.11      |              | (0.70–1.77)                  | (0.70–1.77)                  | 0%     | 0.93          | -                 | -                   |
| Additive              | 1.04   |                         | 1.04      |              | (0.59–1.85)                  | (0.59–1.85)                  | 0%     | >0.9999       | -                 | -                   |
| CsA All               | IL10   | −819C > T               | 2         |              |                               |                               |        |               |                   |                     |
| Dominant              | 1.72   |                         | 1.72      |              | (1.09–2.72)                  | (1.09–2.72)                  | 0%     | 0.33          | -                 | -                   |
| Recessive             | 1.90   |                         | 2.30      |              | (1.12–3.24)                  | (0.82–6.40)                  | 61.9%  | 0.11          | -                 | -                   |
| Additive              | 2.70   |                         | 2.70      |              | (1.43–5.10)                  | (1.43–5.10)                  | 0%     | 0.56          | -                 | -                   |
| CsA All               | IL10   | −592C > A               | 2         |              |                               |                               |        |               |                   |                     |
| Dominant              | 1.67   |                         | 1.67      |              | (1.07–2.60)                  | (1.04–2.70)                  | 13.5%  | 0.28          | -                 | -                   |
| Recessive             | 1.93   |                         | 2.17      |              | (1.16–3.22)                  | (0.91–5.19)                  | 57.6%  | 0.12          | -                 | -                   |
| Additive              | 2.79   |                         | 2.79      |              | (1.52–5.13)                  | (1.52–5.13)                  | 0%     | 0.49          | -                 | -                   |
| CsA All               | TGFB1  | C869T (P10L)            | 2         |              |                               |                               |        |               |                   |                     |
| Dominant              | 0.80   |                         | 0.80      |              | (0.47–1.37)                  | (0.47–1.37)                  | 0%     | 0.67          | -                 | -                   |
| Recessive             | 0.68   |                         | 0.68      |              | (0.44–1.05)                  | (0.44–1.05)                  | 0%     | 0.49          | -                 | -                   |
| Additive              | 0.66   |                         | 0.66      |              | (0.36–1.19)                  | (0.36–1.19)                  | 0%     | 0.94          | -                 | -                   |
| CsA All               | ABCBI1 | 1236C > T rs1128503     | 4         |              |                               |                               |        |               |                   |                     |
| Dominant              | 0.91   |                         | 0.82      |              | (0.59–1.40)                  | (0.32–2.14)                  | 71%    | 0.02          | 0.88              | 0.75                |
| Recessive             | 1.14   |                         | 1.00      |              | (0.72–1.80)                  | (0.38–2.60)                  | 70.5%  | 0.02          | 0.68              | 0.75                |
| Additive              | 1.04   |                         | 0.91      |              | (0.60–1.80)                  | (0.23–3.58)                  | 77.1%  | 0.00          | 0.84              | 0.75                |
| CsA All               | ABCBI1 | 3435 C > T rs1045642    | 3         |              |                               |                               |        |               |                   |                     |
| Dominant              | 1.02   |                         | 1.02      |              | (0.67–1.54)                  | (0.55–1.90)                  | 50.6%  | 0.09          | 0.94              | 0.48                |
| Recessive             | 1.47   |                         | 1.47      |              | (1.01–2.16)                  | (1.01–2.16)                  | 0%     | 0.84          | 0.64              | 0.82                |
| Additive              | 1.33   |                         | 1.37      |              | (0.81–2.18)                  | (0.71–2.67)                  | 33.7%  | 0.20          | 0.70              | 0.48                |
| CsA All               | ABCBI1 | 3435 C > T rs1045642    | 3         |              |                               |                               |        |               |                   |                     |
| Dominant              | 0.44   |                         | 0.44      |              | (0.09–2.16)                  | (0.09–2.16)                  | 0%     | 0.9999        | -                 | -                   |
| Recessive             | 0.98   |                         | 0.98      |              | (0.53–1.82)                  | (0.53–1.82)                  | 0%     | 0.78          | -                 | -                   |
| Additive              | 0.48   |                         | 0.48      |              | (0.09–2.40)                  | (0.09–2.40)                  | 0%     | 0.97          | -                 | -                   |
### Table 6. Meta-analysis results regarding azathioprine.

| Drug     | Gene | Polymorphism | Rs Number | N of Studies | OR with 95% CI Fixed Effects | OR with 95% CI Random Effects | I² (%) | p-Value for Q | Egger Test p-Value | Begg–Mazumdar p-Value |
|----------|------|--------------|-----------|--------------|-------------------------------|-------------------------------|--------|---------------|-------------------|---------------------|
| Azathioprine All | TPMT | 1 vs. 3C | All | 4 | 1.64 (0.83–3.26) | 2.14 (0.22–21.08) | 90.1% | <0.0001 | 0.75 | 0.33 |
|          |      |              | Dominant | | 2.33 (0.24–22.55) | 2.33 (0.24–22.55) | 0% | 0.99 | 0.80 | >0.9999 |
|          |      |              | Additive | | 2.78 (0.29–26.75) | 2.78 (0.29–26.75) | 0% | 0.99 | 0.59 | >0.9999 |
| Azathioprine All | ITPA | 94C > A rs1127354 | All | 2 | 1.60 (0.84–3.06) | 1.59 (0.81–3.14) | 8.6% | 0.30 | - | - |
|          |      |              | Dominant | | 21.82 (1.07–445.72) | 21.82 (1.07–445.72) | 0% | >0.9999 | - | - |
|          |      |              | Additive | | 10.19 (0.92–113.39) | 10.19 (0.92–113.39) | 0% | 0.35 | - | - |

More specifically, with regard to the ABCB1 gene and the three polymorphisms harbored in it, the ABCB1 1236 C > T polymorphism was statistically significant in the studies with prednisolone (PRE) and mycophenolate (MMF). The ABCB1 2677 G > T polymorphism was also statistically significant in the analyses for PRE, whereas the ABCB1 3435 C > T polymorphism was statistically significant in the analyses for MMF and cyclosporine (CsA).

Regarding the genes encoding interleukins, the IL-10 -592 C > A polymorphism in all genetic models and –819 C > T in the dominant and the additive model in the CsA analyses were statistically significant. Another statistically significant polymorphism was the ITPA 94 C > A polymorphism in the recessive model in azathioprine (AZA) analyses. In addition, a statistically significant polymorphism was the MIF -173 G > C polymorphism in the recessive and additive models in PRE analyses.

Regarding heterogeneity control, statistically significant heterogeneity was observed among the studies regarding the CYP2C19*2 polymorphism in the main analysis for cyclophosphamide (CYC): for the TPMT 1 vs. polymorphism, 3C, MIF -173 G > C, Il-6
C-174G for PRE; for TPMT 1 vs. polymorphisms, 3C, ABCB1 1236 C > T, 2677 G > T, for CsA; for TPMT 1 vs. polymorphism 3C for AZA. For tacrolimus (TAC), a statistically significant heterogeneity was observed for polymorphisms ABCB1 2677 G > T and 3435C > T. Due to the statistically significant heterogeneity, the above results should be interpreted with caution, the majority of which are non-statistically significant.

On the existence of a difference in the estimated magnitude of genetic effects in large and small studies (or publication bias), which was assessed using the Egger test for funnel plot asymmetry and the Begg–Mazumdar test based on Kendall’s tau, the test was feasible in meta-analyses involving more than three studies. A statistically significant difference was observed between the MIF -173 G > C polymorphism studies in the PRE analysis.

3. Discussion

The present systematic review and meta-analysis provides the first comprehensive overview of pharmacogenetics studies in CKD regardless of the primary cause of the disease or the treatment. Although the term CKD is a very broad term, only 29 studies were included in the meta-analysis since many studies referred to pharmacokinetics without extractable genetic data. In total, 16 gene polymorphisms located in 11 different genes that were examined in 29 studies were included in the meta-analysis. The key finding of our meta-analysis was that variants ABCB1 (1236 C > T, 2677 G > T, 3435 C > T), IL-10 (-592 C > A, -819 C > T), ITPA (94 C > A), MIF (-173 G > C), and TNF (-308 G > A) gave significant results, suggesting the contribution of these loci to different responses to treatment in patients with CKD.

However, only TPMT has been included in the table of pharmacogenetics biomarkers in drug labeling of the U.S. Food and Drug administration (FDA) for the treatment of AZA [47]. More specifically, homozygous TPMT-deficient patients experience severe myelosuppression. For the other variants, the results are not so robust.

Most studies in the present systematic review are included in the meta-analysis of ABCB1 variants [25,26,29,33–35,37–39,41,45]. These studies included a variety of treatments such as PRE, steroids, CsA, TAC, AZA, sirolimus (SIR), and MMF. It is noteworthy to be mentioned that no study with biologicals was included in the meta-analysis. Regarding calcineurin inhibitors, the effects of ABCB1 3435C > T, 1236C > T, and 2677G > T/A SNPs on the pharmacokinetics of CsA and TAC remain uncertain, with conflicting results. Genetic linkage between these three genotypes suggests that the pharmacokinetic effects are complex and unrelated to any ABCB1 polymorphism. In contrast, it is possible that these polymorphisms may exert a small but combined effect. Any effect is likely to be in addition to the effects of CYP3A5 6986A > G SNP [12].

With regard to the CYP3A5 6986A > G variant, eight studies [23,25,34,36,40,41,44,45] included patients under treatment with pulse CYC, steroids, calcineurin inhibitors, and AZA/SIR. In contrast to CsA, a strong relationship between the CYP3A5 6986A > G SNP and TAC pharmacokinetics was demonstrated in kidney, heart, and liver transplant recipients, as well as in healthy volunteers [12]. Several recent studies have reported an approximate halving of the TAC C0/dose and doubling of the tacrolimus dose requirements in CYP3A5 expressers compared to that in CYP3A5 non-expressers [43,44,48–52].

However, studies with a small number of patients may be responsible for many conflicting results to date. The low frequency of some alleles, such as CYP3A4*1B allele, may not have been sufficient in many cases to detect a difference. In addition, the influence of ethnicity may play a role, as mutated genotypes are often more common in specific ethnic groups. However, even in the same ethnic group, for example in Caucasians, the frequencies of the studied polymorphisms differ. For instance, Caucasians present a minor allelic frequency around 50% regarding the ABCB1 1236C > T polymorphism, whereas the studied TPMT allele frequency polymorphisms range from 0.2–5.5% in Caucasians. Although the genotype itself, rather than the underlying ethnicity, should theoretically detect any differences, it is possible that indeterminate genetic differences (for example, co-inherited SNPs) among Africans, Caucasians, and Asians contribute to significant variables.
In addition, the associations presented in these meta-analyses resulted from pooling a relatively small number of studies and patients with large heterogeneity between studies. Furthermore, the impact of effect modifiers such as age and the pre-treatment cytogenetic and molecular genetic findings was not considered as the individual studies did not provide the relevant data. Indeed, we have not included the analyses of interactions of age and comorbidity in the meta-analysis because these details were not included in the available data. It would be very interesting if future pharmacogenetic studies included this type of data in the analysis. The present systematic review and meta-analysis included studies that varied in terms of treatment and primary cause of CKD, as well as racial descent. Thus, the results should be interpreted with caution. Future studies with more homogenous studies will shed light on the pharmacogenetics in CKD. Thus, lack of significant association in the remaining gene variants does not exclude the possibility of an association.

Last but not least, epigenetic changes in drug metabolizing enzymes, nuclear receptors, and transporters are associated with individual drug responses and acquired multidrug resistance [53]. Consequently, pharmacoepigenetics could provide an explanation for why patients with the same genotype respond differently to therapy with a specific medication. Unrelated to epigenetics, inflammation can significantly influence the extent of CYP suppression, thus contributing to intra- and interindividual variability to drug exposure [54].

4. Materials and Methods

In order to clarify the contribution of the genetic background of CKD patients to the response to medications, a systematic review and meta-analysis of the pharmacogenetic studies reported in CKD patients was performed. The meta-analysis included studies published in English that are indexed in the PubMed database after a search with the terms (“pharmacogenetics” or “pharmacogenomics” or “response” or adverse effects” or “polymorphism” or “treatment”) AND (chronic kidney disease or nephrology or nephropathy or “kidney disease” or “glomerulonephritis”), accessed on 3 August 2020. In addition, all the references cited in the studies as well as the published meta-analyses that are relevant to the topic were also reviewed for any studies not indexed in PubMed. Unpublished data were not requested from any author.

The inclusion criteria that studies had to meet were: (a) included patients with CKD who did not respond to treatment or patients with CKD who had side effects due to medication (non-responders); (b) included patients with CKD who responded to treatment or patients with CKD who had no side effects due to medication (responders); (c) provided complete genotypic data by genotype for both responders to treatment and non-responders or allele frequencies, excluding studies that presented merged genotypic data.

Case reports, editorials, review articles, and publications with other study designs, such as family-based studies, were excluded. In studies with overlap, the most recent and largest study with data was included in the meta-analysis. Only studies using validated genotyping methods were considered. The eligibility of the studies was assessed independently by two researchers, the results were compared and any disagreement was resolved.

From each study, the following information was extracted: first author, year of publication, nationality of the study population, demographics, sample matching, and genotypic data of respondents and non-responders.

The association between genotype distribution and response to medication was examined using the dominant, recessive, and additive inheritance models. For all associations, the odds ratios (OR) with the corresponding 95% confidence intervals (CI) were recorded. A pooled OR was calculated based on the individual ORs. The threshold for meta-analysis was two studies per polymorphism. The pooled OR was calculated using fixed effects (FE) (Mantel–Haenszel) and random effects (RE) (DerSimonian and Laird) models. The random effects model assumes a genuine diversity in the results of the various studies and incorporates it into the variance calculations between studies. Heterogeneity between studies was tested using Cochran’s Q statistic (considered statistically significant at \( p < 0.10 \)). Heterogeneity was quantified by measuring \( I^2 = (Q - df)/Q \), which is independent of
the number of studies included in the meta-analysis. We also tested for small study effects with the Egger test and the Begg–Mazumdar test based on Kendall’s tau. Cumulative meta-analysis and retrospective meta-analysis were performed for each polymorphism to assess the trend of pooled OR over time.

For each study, we examined whether controls confronted with Hardy–Weinberg equilibrium (HWE) predicted genotypes using Fisher’s exact test. Finally, subgroup analyzes were performed based on ethnicity.

5. Conclusions

In conclusion, there is strong evidence that variants in the ABCB1, IL-10, ITPA, MIF, and TNF genes are related to poor response and/or adverse drug reactions in patients with CKD. Future studies would be required to confirm the results of the present meta-analysis, and an appropriate computer program could help guide the selection of the best drugs and doses.

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Abbreviations

Chronic kidney disease — CKD
Kidney Disease Outcomes Quality Initiative — KDOQI
Mammalian target of rapamycin inhibitors — mTORs
Cyclosporine — CsA
Tacrolimus — TAC
Sirolimus — SIR
Azathioprine — AZA
Mycofenolic acid — MPA
Mycofenolate — MMF
ATP binding cassette subfamily B member 1 — ABCB1
cytochrome P450 family 2 subfamily C member 9 — CYP2C9
cytochrome P450 family 2 subfamily C member 19 — CYP2C19
cytochrome P450 family 3 subfamily A member 5 — CYP3A5
interleukin 6 — IL-6
interleukin 10 — IL-10
inosine triphosphatase — ITPA
macrophage migration inhibitory factor — MIF
transforming growth factor beta 1 — TGFß1
tumor necrosis factor — TNF
thiopurine S-methyltransferase — TPMT

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