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Correlation between gene polymorphism and blood concentration of calcineurin inhibitors in renal transplant recipients

An overview of systematic reviews

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Abstract

Background: To provide an overview of systematic reviews and meta-analyses (SRs/MAs) of the correlation between genetic polymorphisms and blood concentrations of calcineurin inhibitors (CNIs) in recipients of renal transplant.

Methods: Databases including Medline, EMBase, The Cochrane Library (Issue 7, 2016), the Chinese Biomedical Literature Database, the China National Knowledge Infrastructure, the China Science and Technology Journal Database, and the Wan Fang Database were searched for SRs/MAs of the correlation between genetic polymorphisms and blood concentrations of CNIs in renal transplant recipients from inception to July 2016. Two reviewers independently screened the literatures and extracted data, then the AMSTAR measurement tool was used to assess the methodological quality of SRs/Mas included in the overview.

Results: Fourteen SRs/MAs met the inclusion criteria. The most commonly reported genotype was CYP3A5*3/*3, which was strongly associated with cyclosporine A (CsA) and tacrolimus (FK506). MDR1 C3435T CC was also associated with CNI use, especially with CsA therapy. Other less commonly reported genotypes such as CYP3A4*1B, MDR1 C1236T CC, and MDR1 G2677T/A GG also affected the blood concentrations of CNIs.

Conclusions: Our overview showed that polymorphisms influence the blood concentrations of CNIs, which suggests the necessity to monitor these concentrations in patients with genotypes that affect dose-adjusted trough concentrations (C_0/D) or dose-adjusted peak concentrations (C_2/D) to regulate the dosage for individual administration. Because of the limited number of included studies, these findings should be verified in more high-quality studies.

Abbreviations: 95% CI = 95% confidence interval, AMSTAR = assessing the methodological quality of systematic reviews, C2/D = dose-adjusted peak concentrations, CNI = calcineurin inhibitor, CsA = cyclosporine A, FK506 = tacrolimus, m = month, MDR1 = multi-drug resistance gene, NR = non report, SRs/MAs = systematic reviews/meta-analyses, w = week, WMDs = weighted mean difference.

Keywords: calcineurin inhibitor, gene polymorphisms, overview of systematic reviews, renal transplant

1. Introduction

More than 2 million people worldwide suffer from end-stage kidney disease requiring renal replacement therapy,[1] and the kidney transplantation is considered as a superior renal replacement therapy to dialysis.[2] Calcineurin inhibitors (CNIs) can effectively prevent rejection after transplantation and have been widely used in clinical practice as a first-line immunosuppressant after renal transplantation, including tacrolimus (FK506), and cyclosporine A (CsA). However, the range of effective blood concentrations of these drugs is narrow and the individual differences of pharmacokinetic are relatively large. Moreover, even when conventional regimens are used, organ transplant rejection or drug-related toxicity often occurs. Therefore, it is necessary to monitor these blood concentrations to adjust the dosage for individual administration.

Genetic polymorphisms are thought to be the main reason for individual differences in the immune effects of CNIs, including CYP3A4, CYP3A5, and drug transporter P-glycoprotein.[3,4] Therefore, it is important to determine the influence of polymorphisms on CNI blood concentrations. With the development of pharmacogenomics, increasing attention is being paid to the study of polymorphisms of drug metabolizing enzymes, drug transporters, and drug targets. Therefore, we performed an overview of systematic reviews and meta-analyses to evaluate the relationship between polymorphisms in renal transplant recipients and the blood concentrations of CNIs. The goal of this study was to provide clinicians with an unbiased,

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quantitative summary of the effect of polymorphisms on CNI blood concentrations to facilitate shared decision-making when discussing CNI therapy with their patients.

2. Materials and methods

2.1. Definitions and inclusion criteria

This overview was approved by the Ethics Committee of West China Hospital, Sichuan University. This overview conducted according to an a priori protocol that adhered to preferred reporting items for systematic reviews and meta-analyses standards for the conduct and reporting of systematic reviews.[5] The explicit research question, framed in a population, intervention, comparison, and outcome format, was reviewed to determine the effects of different genotypes of renal transplant recipients, such as CYP3A4, CYP3A5, and MDR1, on blood concentrations of drugs. Our target population was humans, so studies limited to animals were excluded.

2.2. Search criteria

An electronic search of Medline, EMBase, The Cochrane Library (Issue 7, 2016), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wan Fang Database was performed by a professional information specialist of all articles from inception through July 2016. The search terms "kidney transplantation" and "genotype" were used, limiting results to systematic reviews and meta-analyses in English and the Chinese language. Abstracts were excluded if they were not reviews, were limited exclusively to animals, or had a focus other than the effect of different genotypes of renal transplant patients on blood concentrations of CNIs.

2.3. Screening process and methods

The search identified 162 studies (Fig. 1), of which 104 were unique. Two reviewers independently assessed the initial dataset to ensure that the studies were systematic reviews or meta-analyses. We excluded studies from further consideration if exact search criteria were not provided or if there was no mention of dual data extraction by 2 independent reviewers to reduce bias. Two reviewers independently abstracted data from the included articles using a standardized form and resolved any discrepancies through mutual discussion and re-review of the relevant full-text article.

2.4. Evaluation of the included studies

Methodological quality was assessed with the assessing the methodological quality of systematic reviews (AMSTAR) scale, an externally valid and reliable 11-item questionnaire with "yes," "no," "can't answer," and "not applicable" choices.[6] Each of the 14 included articles was given a score out of 11 points, with 1 point given for each "yes" and 0 points given for any other

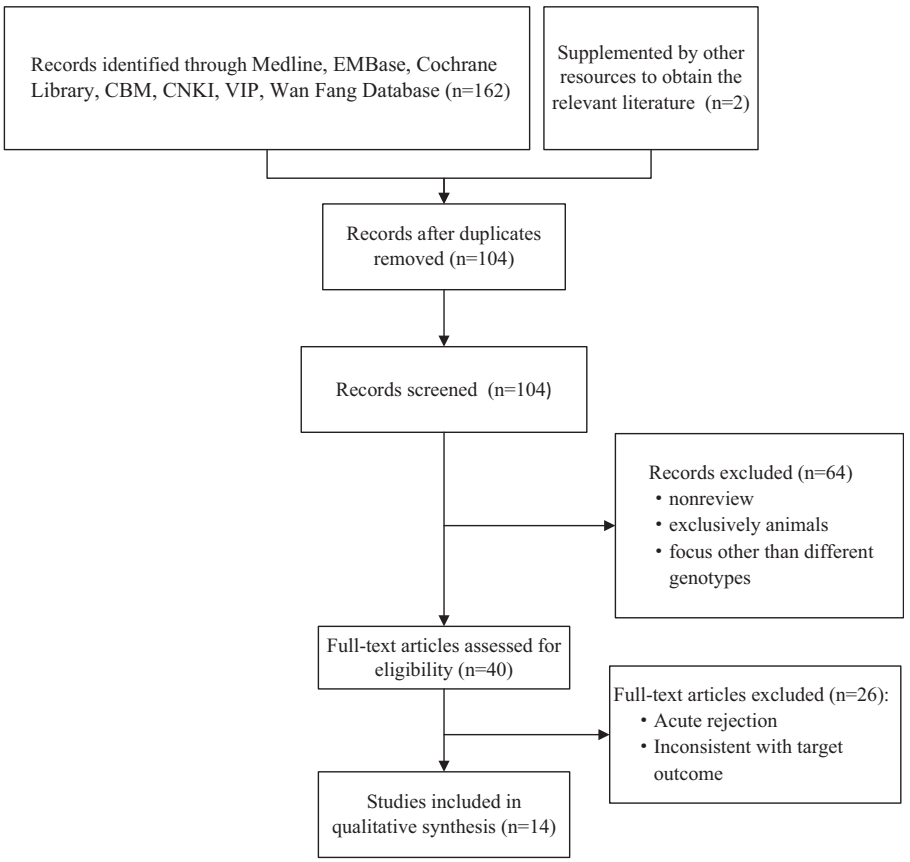

Figure 1. Flowchart of article selection for the final dataset used in the meta-analysis.

Table 1

Characteristics of included studies.

Author year	Country	Search date	Ethnic	No. studies (participants)	Target gene	follow-up	Type of CNI	AMSTAR Score
Shi 2015[9]	China	2014.02	Asian	7 (750)	CYP3A4*1G	<2 w, 1 m, 2–3 m	FK 506	6
Shi 2015[10]	China	2014.09	Caucasian, Indian	7 (1182)	CYP3A4*1B	1 w, 1, 3, 6, 1 m	FK 506	10
Zhu 2011[11]	China	2009.12	Asian, Caucasian, Indian, Chineses	14 (1742)	CYP3A5*3	NR	CsA	8
Tang 2010[12]	China	2010.03	Caucasian, African, Asian, Chinese, North Indian	14 (1821)	CYP3A5*3	2 w, 1 m, 3, 6, 12 m	CsA	8
Fu 2013[13]	China	2013.07	Chinese, Korean, Italian, Argentine, Indian	12 (956)	CYP3A5*3	1 w, 1, 3, 6, 12 m	FK 506	9
Rojas 2015[14]	Chile	2013.10	Asian, Caucasian, Indian, African	32 (2732)	CYP3A5*3	1 w, 2 w, 1 m, 3, 6, 12 m	FK 506	10
Tang 2011[15]	China	2009.8	White, Japanese, Chinese, North Asian Indian	23 (1779)	CYP3A5*3	2 w, 1 m, 3 m, 6 m, 12 m	FK 506	9
Terrazzino 2012[16]	Italy	2011.09	White, Asian	24 (NR)	CYP3A5*3 MDR1 C3435T	1 m, 3–6 m, 12–24 m	FK 506	10
Tang 2010[17]	China	2008.10	South Asian, Caucasian, Indian, Chineses	7 (605)	MDR1 C1236T	NR	CsA	7
Lee 2015[18]	China	2014.07	Asian, Caucasian, Indian, Black, Chineses	13 (1293)	MDR1 C3435T	1 w, 1–3 m, >6 m	CsA	9
Li 2012[19]	China	2011.12	Chineses	13 (893)	MDR1 C3435T	1 w, 1 m, 12 m	CsA	9
Li 2012[20]	China	2011.07	Asian, Caucasian, Black, Chineses	13 (1327)	MDR1 C3435T	1, 3, 6, 12 m	FK 506	9
Wang 2015[21]	China	2014.03	Asian	8 (826)	MDR1 C3435T	1, 3, 6, 12 m	FK 506	9
Tang 2010[22]	China	2008.10	Caucasian, Caribbea Caucasian, Indian, South Asian, Chinese	7 (844)	MDR1 G2677T/A	1, 3, 6, 12 m	CsA	8

AMSTAR = assessing the methodological quality of systematic reviews, CNI = calcineurin inhibitor, CsA = cyclosporine A, FK506 = tacrolimus, m = month, NR = non report, w = week.

option. If there was disagreement between the reviewers, the "can't answer" option was selected and no points were awarded.

2.5. Data synthesis

Descriptive information collected for each systematic review included the country of origin, the number of studies in the review, the types of studies included (randomized controlled trials, cohort studies, or case reports), adult or children/adult populations, and the type of data reported (qualitative, quantitative, pooled, or nonpooled). Quantitative information included the pooled weighted mean difference (WMDs) or standard mean difference and 95% confidence intervals reported in the systematic review. Because the purpose of this study was to overview existing systematic reviews, we did not attempt to reanalyze original data or conduct new meta-analyses by combining studies from different reviews.

3. Results

3.1. SR search and screening results

Database search strategies yielded 164 records, added 2 records (acquire relevant literature through supplements with other resources),[7,8] and 60 duplicates were identified and excluded. We also excluded 104 citations after screening the titles and abstracts; thus, the full texts of the remaining 40 citations were retrieved for further assessment. Eleven publications were excluded because of acute rejection, and 14 were excluded for being inconsistent with the target outcome. Thus, a total of 14 SRs were included in this overview. Details of the literature search and selection can be found in Fig. 1.

3.2. Characteristics of included SRs

Fourteen reviews met the inclusion criteria. These studies were published between 2010 and 2015, and 5 were published in the past 3 years. The most common country of origin was China (n = 10). The number of source articles included in each review ranged from seven to 32, with a median of 13. FK506 was assessed as a treatment in 8 reviews, while CsA was assessed in the remaining 6. Seven reviews reported genotypes for *CYP3A*, 6 reported *MDR1* genotypes, and the last review reported both *CYP3A* and *MDR1* genotypes. SR characteristics are shown in Table 1.

3.3. Methodological quality of included SRs

AMSTAR quality scores for the reviews ranged from 7 to 10, with 64% of reviews achieving a score of 9 or 10. All reviews were reproducible in selection and data extraction, provided the characteristics of the included studies and the used appropriate methods to combine study findings. More than 90% of reviews used priori protocols, provided lists of studies (included and excluded), and formulated conclusions with appropriate study quality. Conversely, only half of the reviews described the conflicts of interest (50%). Furthermore, many did not assess publication bias (21%) or assess and document the scientific quality of included studies (43%). AMSTAR criteria for the methodological quality of included studies are shown in Table 2.

3.4. Relationship between genotypes and blood concentration

Cytochrome P-450 CYP3A. Eight systematic reviews[9–16] stated the *CYP3A* genotype: 2 [9,10] were *CYP3A4* and the

Table 2

AMSTAR criteria for methodological quality of included studies*.

Criteria†	Yes	No	Unsure
Was an "a priori" design provided?	13 (93)	1 (7)	0
Was there duplicate study selection and data extraction?	14 (100)	0	0
Was a comprehensive literature search performed?	12 (86)	2 (14)	0
Was the status of publication used as an inclusion criterion?	12 (86)	2 (14)	0
Was a list of studies (included and excluded) provided?	13 (93)	1 (7)	0
Were the characteristics of the included studies provided?	14 (100)	0	0
Was the scientific quality of included studies assessed and documented?	6 (43)	1 (7)	7 (50)
Was study quality used appropriately in formulating conclusions?	13 (93)	1 (7)	0
Were the methods used to combine study the findings appropriate?	14 (100)	0	0
Was the likelihood of publication bias assessed?	3 (21)	11 (79)	0
Was the conflict of interest included?	7 (50)	7 (50)	0

AMSTAR = assessing the methodological quality of systematic reviews.

* Values presented in n (%).

† Content in Criteria column from Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007;7:10. © Shea et al. This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

remaining 6 [11–16] were *CYP3A5* (Table 3). All reviews investigated the effect of *CYP3A* polymorphisms on CNI C_0/D, while 1 review[11] investigated the effect of *CYP3A* polymorphisms on CNI C_2/D. In 2 systematic reviews,[9,10] the C_0/D for FK506 of CYP3A4*1G and CYP3A4*1B was lower than that for CYP3A4*1/*1. However, the results of 1 study were questionable because of problems with data pooling. For example, in subgroup analyses of fewer than 14 days, the authors included all data for fewer than 14 days in the same study. We, therefore, re-analyzed these data, and obtained a WMD of 45.16, $P < .00001$. Six reviews[11–16] showed that the C_0/D of CYP3A5*3/*3 was higher compared with that of CYP3A5*1, and 1 review[11] showed that patients carrying the CYP3A5*3/*3 genotype would require a lower dose of CsA to reach target levels compared with CYP3A5*1/*1 or *1/*3 carriers because of the higher C_2/D. Details of these results are shown in Table 3.

Multi-drug resistance gene (MDR1). Seven systematic reviews[16,17–22] stated the *MDR1* genotype: 5[16,18–21] were *MDR1* C3435T and the remaining 2[17,22] were *MDR1* C1236T and *MDR1* G2677T/A. All reviews investigated the effect of *MDR1* polymorphisms on CNI C_0/D. Of 5 reviews[16,18–21] with genotype *MDR1* C3435T and CNI cyclosporin A or FK506, 2 reviews [18,19] of cyclosporin A showed that the C_0/D of CC carriers was lower than that of TT carriers, 1 review[20] of FK506 showed that the C_0/D of CC carriers was lower than that of TT carriers or CT carriers, and 2 reviews[16,21] of FK506 showed no significant difference between CC carriers and CT or TT carriers. In a review[17] of genotype *MDR1* C1236T with cyclosporin A, there was no significant difference between CC carriers and CT or TT carriers. However, *MDR1* G2677T/A GG carriers were shown to require a higher dose of cyclosporin A to reach target levels compared with other carriers. Details of the results are shown in Table 4.

Four reviews[17–19,22] investigated the effect of *MDR1* polymorphisms on CNI C_2/D for cyclosporin A. The genotype in 2 reviews[18,19] was *MDR1* C3435T; 1 showed that CC carriers reduced the C_2/D to a greater extent than TT carriers, while the other revealed no significant difference between CC carriers and CT or TT carriers. The review of the *MDR1* C1236T genotype showed that CC carriers reduced the C_2/D to a greater extent than TT carriers, while the review of the *MDR1* G2677T/A genotype showed that GG carriers also reduced the C_2/D to a

Table 3

Effect of CYP3A gene polymorphism on CNI C_0/D.

Author year	AMSTAR Score	Type of CNI	Target gene	Intervention vs Control (C_0/D)	95% CI	*P*
Shi 2015[9]	6	FK 506	CYP3A4*1G	*1/*1 vs *1G	45.16 (33.12, 57.19)#	$P < .00001$
Shi 2015[10]	10	FK 506	CYP3A4*1B	*1/*1 vs *1B	62.219 (14.218,110.221)	$P = .011$
Zhu 2011[11]	8	CsA	CYP3A5*3	*1 vs *3/*3	-3.75 (-7.58, 0.07)	$P = .054$
Tang 2010[12]	8	CsA	CYP3A5*3	*1/*3 vs **1/*1	1.93 (-3.40, 7.25)	$P = .48$
				*3/*3 vs *1/*1	10.06 (3.12, 17.00)	$P = .004$
Fu 2013[13]	9	FK 506	CYP3A5*3	*1/*1 vs *1/*3	-19.51 (-29.84, -9.18)	$P = .0002$
				*1/*1 vs *3/*3	-78.32 (-123.02, -33.61)	$P = .0006$
				*1/*3 vs *3/*3	-79.72 (-95.06, -64.38)	$P < .00001$
Rojas 2015[14]	10	FK 506	CYP3A5*3	3*3 vs *1	61.29 (46.00, 76.58)	$P < .00001$
Tang 2011[15]	9	FK 506	CYP3A5*3	3*3 vs *1	0.044 (0.020–0.068)	$P < .001$
Terrazzino 2012[16]	10	FK 506	CYP3A5*3	3/*3 vs *1/*1+ *1/*3 *1/*3 vs *1/*1	63.57 (50.85, 76.30)	$P < .001$
					19.83 (13.86, 25.80)	$P = .174$

95% CI = 95% confidence interval, AMSTAR = assessing the methodological quality of systematic reviews, C_0/D = dose-adjusted trough concentrations, CNI = Calcineurin inhibitor, CsA = cyclosporine A, FK506 = tacrolimus.

the re-analysis WMD and 95%CI.

Table 4

Effect of MDR1 gene polymorphism on CNI C_0/D.

Author Year	AMSTAR Score	Type of CNI	Target gene	Intervention vs Control (CO/D)	95% CI	*P*
Tang 2010[17]	7	CsA	MDR1 C1236T	CC vs CT	−0.28 (−8.02, 7.47)	*P*=.94
				CC vs TT	−6.09 (−14.84, 2.65)	*P*=.17
Lee 2015[18]	9	CsA	MDR1 C3435T	CC vs CT	3.18 (−1.02, 7.39)	*P*=.14
				CC vs TT	4.18 (1.00, 7.37)	*P*=.01
				CT vs TT	0.95 (3.69, 5.60)	*P*=.69
Li 2012[19]	9	CsA	MDR1 C3435T	CC vs CT	−25.09 (-26.39, -23.79)	*P*<.00001
				CC vs TT	-15.86 (-24.45, −7.26)	*P*=.0003
Li 2012[20]	9	FK 506	MDR1 C3435T	CT vs CC	12.60 (−21.39, 46.60)	*P*=.47
				CC vs TT	3.56 (-27.72, 34.84)	*P*=.82
				CT vs TT	15.93 (-16.80, 48.67)	*P*=.34
Wang 2015[21]	9	FK 506	MDR1 C3435T	CC vs CT	−8.63 (−15.87, −1.39)	*P*=.02
				CC vs TT		*P*=.07
				CT vs TT	−10.53 (–22.05, 1.00)	*P*=.06
					−5.20 (-10.57, −0.16)	
Terrazzino 2012[16]	10	FK 506	MDR1 C3435T	CT+TT vs CC	12.62 (– 2.54, 27.79)	*P*=.255
				TT vs CC+CT	9.64 (– 11.44, 30.72)	*P*=.052
Tang 2010[22]	8	CsA	MDR1 G2677T/A	GG vs GT+GA	−14.13 (-22.55, -5.72)	*P*=.001
				GG vs TT+TA+AA	−19.15 (-28.52, -9.79)	*P*<.001

95% CI = 95% confidence interval, AMSTAR = assessing the methodological quality of systematic reviews, C_0/D = dose-adjusted trough concentrations, CNI = Calcineurin inhibitor, CsA = cyclosporine A, FK506 = tacrolimus.

greater extent compared with other carriers[17] Details of the results are shown in Table 5.

4. Discussion

An overview of systematic reviews of evidence-based medicine is a comprehensive method of examining studies of the etiology, diagnosis, treatment, or prognosis of the same disease or health problem. It can identify methodological bias and the quality of evidence for the conclusions of systematic review, providing more centralized high-quality evidences for decision makers. The introduction of evidence-based medicine in the field of genetic polymorphisms will help improve the safety and efficacy of immunosuppressive therapy.

Immunosuppressive agents are often used to prevent transplant rejection after organ transplantation. Long-term use of these agents results in efficacy differences between patients, mainly through non-genetic factors such as liver and kidney function and drug interactions. However, these factors can only explain individual differences in the pharmacokinetics of immunosuppressive agents. Additional factors such as polymorphisms in pharmacokinetic-related genes such as drug-metabolizing enzymes and drug transporter genes further explain these differences.

Cyclosporine A and FK506 are mostly metabolized by the liver and gastrointestinal tract and cytochrome P450 isoenzyme systems. The transportation of the 2 drugs largely involves the multidrug resistance protein, while metabolism and clearance mainly occur through CYP enzymes, especially CYP3A4 and CYP3A5.[9,10] Polymorphisms in the genes encoding these proteins can lead to different phenotypes and is the main reason for individual differences in drug metabolism rate.

Our study identified several genotypes that are significantly associated with CNI use, including CYP3A5*3/*3, CYP3A4*1B, *MDR1* C3435T CC, *MDR1* C1236T CC, and *MDR1* G2677T/A GG. The most commonly reported genotype was CYP3A5*3/*3, which was strongly associated with CsA and FK506. The reviews showed that patients carrying the CYP3A5*3/*3 genotype would require lower doses of CsA or FK506 to reach target levels compared with CYP3A5*1/*1 or

Table 5

Effect of MDR1 gene polymorphism on CNI C_2/D.

Author Year	AMSTAR Score	Type of CNI	Target gene	Intervention vs Control (CO/D)	95% CI	*P*
Tang 2010[17]	7	CsA	MDR1 C1236T	CC vs CT	−10.33 (-21.17, 0.51)	*P*=.06
				CC vs TT	−24.52 (-46.96, −2.07)	*P*=.032
Lee 2015[18]	9	CsA	MDR1 C3435T	CC vs CT	13.96 (−0.72, 28.64)	*P*=.06
				CC vs TT	20.85 (2.25, 39.46)	
				CT vs TT	7.44 (9.27, 24.16)	*P*=.03
						P=.38
Li 2012[19]	9	CsA	MDR1 C3435T	CC vs CT	1.68 (−14.59, 17.95)	*P*=0.84
				CC vs TT	8.95 (-11.63, 29.53)	*P*=.39
Tang 2010[22]	8	CsA	MDR1 G2677T/A	GG vs GT+GA GG vs TT+TA+AA	−6.37 (−12.92, 0.18)	*P*=.06
					−28.39 (-42.88, −13.91)	*P*=.001

95% CI = 95% confidence interval, AMSTAR = assessing the methodological quality of systematic reviews, C_2/D = dose-adjusted peak concentrations, CNI = Calcineurin inhibitor, CsA = cyclosporine A, FK506 = tacrolimus.

*1/*3 carriers. *MDR1* C3435T CC was also associated with CNI use, especially CsA therapy. Two reviews of cyclosporin A showed that patients carrying the CC genotype would require higher doses of CsA to reach target levels compared with TT carriers. Other less commonly reported genotypes such as CYP3A4*1B, *MDR1* C1236T CC, and *MDR1* G2677T/A GG could also affect the blood concentrations of CNI. Notably, even the important role of gene polymorphism has been revealed by growing studies, according to the current clinical experience, gene testing is relatively rare, so further practical research is needed.

There are several limitations to the present study. First, because this study was an overview of systematic reviews, we may have overlooked polymorphisms associated with CNIs that were published as individual studies or case reports. However, our intent was to identify and focus on those genotypes that were reported with sufficient frequency to justify systematic reviews, which yielded robust information on CYP3A5*3/*3 and *MDR1* C3435T CC. This is further limited because most studies did not state the CNI dose so as such could not be further analyzed. Second, which is common to all overview studies, is the potential redundancy (overlap) of articles included in individual systematic reviews. Because of the risk of publication bias and the differences in the nature of the data presented, differences in effect size as they relate to study type could not be established. Finally, our study did not describe the effect of polymorphisms on CNI blood concentrations among ethnic groups. These effects, though important, were outside the scope of our overview. Of note, while strictly pediatric studies were excluded from our analysis, none of the studies with mixed populations separated pediatric and adult populations in their analyses. Future studies may better delineate these differences, if any.

In summary, our overview of systematic reviews demonstrated the consistent and clinically important impact of CYP3A5*3/*3 and *MDR1* C3435T CC on CNI therapy.

Author contributions

Data curation: Lan Su, Lu Yin, Jinkun Yang.
Formal analysis: Lu Yin.
Methodology: Lan Su, Jinkun Yang.
Supervision: Lin Sun.
Writing – original draft: Lan Su.
Writing – review & editing: Lin Sun.

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