Effects of *CYP3A5* polymorphisms on tacrolimus pharmacokinetics in pediatric kidney transplantation: a systematic review and meta-analysis of observational studies

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Background: ***CYP3A5*** **genetic polymorphisms have been reported to be strongly associated with the tacrolimus pharmacokinetics in adult kidney transplantation. However, there is no published meta-analysis in the influence of** ***CYP3A5*** **variants on the requirements of the tacrolimus dose in pediatric renal-transplant recipients (RTRs). We wished to determine the effects of** ***CYP3A5*** **polymorphisms on tacrolimus pharmacokinetics in pediatric RTRs.**

Methods: **A literature search was conducted to include relevant articles by searching PubMed, EMBASE and the Cochrane Central Register of Controlled Trials. Pharmacokinetic-associated parameters such as dose administration, as well as concentrations and dose-adjusted concentrations of tacrolimus were extracted and the meta-analysis undertaken.**

Results: **The meta-analysis involved four studies and one study series involving 268 pediatric RTRs. A significant difference was observed in the mean trough concentration/dose of tacrolimus between recipients carrying** ***CYP3A5*3/*3*** **variants (referred to as "non-expressers") and those carrying** ***CYP3A5*1*** **(referred to as "expressers") [standard mean difference (SMD)=-1.09, 95% confidence interval (CI): -1.92 to -0.25,** ***P*****=0.011]. Moreover, significance was observed in the mean daily dose of tacrolimus between non-expressers and expressers in pediatric RTRs (SMD=0.44, 95% CI: 0.20 to 0.68,** ***P*****<0.001).**

Conclusion: **Our meta-analysis identified a positive correlation between** ***CYP3A5*** **genotypes and tacrolimus pharmacokinetics in pediatric RTRs.**

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Key words: ***CYP3A5*****; kidney transplantation; meta-analysis; pediatric; tacrolimus**

Introduction

Tacrolimus is a potent macrolide immunosuppressive agent. It has been administered widely in pediatric/adult kidney transplantation for the prevention of allograft rejection. Tacrolimus inhibits cellular and T-lymphocyte-dependent responses through inactivation of the intracellular calcineurin complex.[1] Tacrolimus is characterized by a narrow therapeutic index and variable oral bioavailability. Hence, therapeutic drug monitoring (TDM) is done regularly to optimize its efficacy and to avoid toxicity. TDM has shown that various patient-specific factors (e.g., genes) may be involved in the metabolism and disposition of tacrolimus, suggesting that dose should be "tailored" to individual patients.[2]

Tacrolimus is metabolized by members of the CYP3A family of drug-metabolizing enzymes, especially CYP3A4 and CYP3A5.[3] Numerous studies have reported a strong relationship in pediatric kidney transplantation between exposure to a tacrolimus dose and *CYP3A5* genotype polymorphisms such as the *CYP3A5*1* allele and *CYP3A5*3* allele.[4-6] More importantly, the latter has been described to result in the absence of protein activity, whereas recipients with at least one *CYP3A5*1* allele may express the CYP3A5 enzyme.[7] However, various factors related to the ontogeny of drug disposition (absorption, distribution, metabolism and excretion) can also contribute to the variability in the requirement of the tacrolimus dose in pediatric recipients, rather than the influence of

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genetic polymorphisms. Recent studies have shown that higher tacrolimus doses are required to achieve the same target concentration in children aged <12 years compared with those aged >12 years in the first 2 weeks after transplantation.[5,8] Therefore, the contribution of *CYP3A5* genetic polymorphisms to the metabolism of tacrolimus exposure in pediatric kidney transplantation is not known.

Our meta-analysis aimed to evaluate the influence of a single nucleotide polymorphism (SNP) of *CYP3A5* on tacrolimus pharmacokinetics in pediatric kidney transplantation during the first year after transplantation.

Methods

Literature search

A comprehensive literature search was performed to identify relevant studies in PubMed, the Cochrane Central Register of Controlled Trials, Embase, the China CNKI and WANFANG databases (updated on Aguest 1, 2016). Search items were: mesh term "kidney transplantation"; mesh term "child"; "polymorphism", "genetic polymorphism" or "single nucleotide polymorphism" or "SNP" or "gene mutation" or "genetic variants"; "tacrolimus" or "FK506"; "CYP3A5" or "cytochrome P450 3A5". Furthermore, the reference lists of all studies included in the meta-analysis, as well as the abstracts of annual meetings of the American Society of Nephrology, the International Transplant Society and the European Dialysis and Transplantation Association, were reviewed. If there were more than one articles published with the same content, we will choose the most complete one.

Inclusion and exclusion criteria

To include relevant studies in our meta-analysis, three main criteria were used. First, trough concentrations of tacrolimus were measured separately in pediatric renal-transplant recipients (RTRs) with three genotypes (*CYP3A5*1/*1*, **1/*3* and **3/*3*), or separately in *CYP3A5*3/*3* and **1/*3+*1/*1* genotypes. Second, tacrolimus concentrations should be adjusted or could be estimated by the corresponding 24-hour dose on the basis of mg/kg. Third, the results of each study were expressed (or could be estimated) as the mean and standard deviation (SD). If such information was missing, we contacted the authors of the eligible studies. If we did not receive the requisite data, we excluded the study. Exclusion criteria were: 1) case reports; 2) reviews; 3) studies in which outcomes were not separated on basis of *CYP3A5* genotypes; 4) studies in a language other than English. Two authors (ZYP and WZJ) reviewed articles independently for potential inclusion in our meta-analysis.

Data extraction and quality assessment

According to the inclusion and exclusion criteria stated above, all titles and abstracts identified in the literature search for potentially eligible studies were evaluated independently by two authors (ZYP and WZJ). A standard form was used for each of these included studies. The following information was extracted: first author, year of publication, ethnicity; number of patients, age, sex, measurement methods for the trough concentration of tacrolimus (C_0) and *CYP3A5* genotype, initial daily dose of tacrolimus, dose-adjusted concentration of tacrolimus (C_0/dose), time-courses for measurement of tacrolimus concentrations. If data were expressed as subjects with three genotypes, a statistical method reported from the Cochrane Handbook[9] was applied to estimate the mean (SD).

The quality of included studies was assessed by two independent reviewers (WZJ and ZCC) through a checklist derived from the Strengthening the Reporting of Genetic Association recommendations for reports on genetic-association studies,[10] and modified according to a quality checklist described elsewhere.[11]

Statistical analyses

Pooled data were used to evaluate the strength of the relationship between genotypes and tacrolimus pharmacokinetics using the standard mean difference (SMD) with 95% confidence intervals (95% CIs). $P<0.05$ was considered significant. Heterogeneity among trials was determined by I^2, which was defined as: $100\%\times(Q-df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom, with a fixed-effect model set at low statistical inconsistency ($I^2<25\%$); otherwise, we selected a random-effects model, which is better adapted to clinical and statistical variations.[12] Sensitivity analysis was done to evaluate the stability of the meta-analysis, which was conducted by omitting one study at a time to test its influence on the overall estimate. We planned to explore heterogeneity by conducting subgroup analysis on the basis of time-courses of transplantation and ethnicity. A test of interaction described by Altman et al[13] was used to determine the significance of the differences between subgroups. All statistical analyses were undertaken using Stata version 12.0 (Stata, College Station, TX, USA).

Results

Study inclusion and basic characteristics

Twenty abstracts from multiple databases were searched, nine of which were excluded based on their titles and abstracts (Fig. 1). The remaining 11 original full-text articles were retrieved for further assessment, and four were excluded for non-conformity with inclusion criteria. As a result, four clinical studies[14-17] and one study series[7,18,19] involving 268 pediatric RTRs were included in our meta-analysis. Among these eligible studies, two studies and one study series were

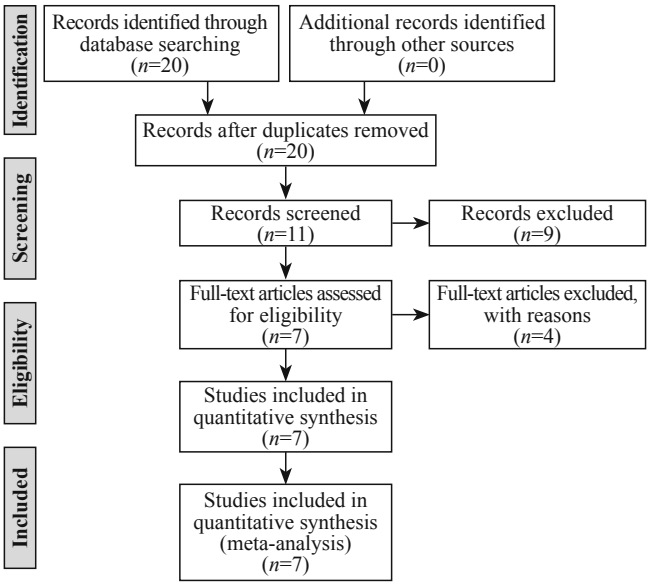

Fig. 1. Flow diagram of eligible studies in our meta-analysis.

from Caucasian populations, one study was from Asian population, and one was from a Latino population. In addition, three of the eligible studies[14,18,19] did not provide evidence of the Hardy-Weinberg equilibrium (HWE), thereby contributing to heterogeneity in our meta-analysis. Basic characteristics of included studies are summarized in Table 1. Outcomes of quality assessment of all eligible studies are shown in Table 2.

Genotype and tacrolimus pharmacokinetics in pediatric RTRs

Results derived from the meta-analysis of the dose-adjusted trough concentration of tacrolimus (C_0/dose) and the *CYP3A5*3* variant are summarized in Table 3. When all studies were combined in our initial analysis, regardless of the time-courses of transplantation, there was a significant difference in the mean C_0/dose of tacrolimus between recipients carrying *CYP3A5*3/*3* variants (referred to as "non-expressers") and those carrying *CYP3A5*1* (referred to as "expressers") (SMD=-1.09, 95% CI: -1.92 to -0.25, *P*=0.011) (Fig. 2). Significance was observed in the mean daily dose of tacrolimus between the non-expressers group and expressers group in pediatric RTRs (SMD=0.44, 95% CI: 0.20 to 0.68, *P*<0.001) (Fig. 3). Furthermore, additional subgroup analysis was done to explore potential sources of such high heterogeneity. In the subgroup analysis of mean C_0/dose, no statistical association at 7 days, 14 days, 1 month, 3 months or 12 months between expressers and non-expressers was found (Table 3, Fig. 2). In the subgroup analysis of mean daily dose, a significant difference was also observed at 14 days and 12 months between the two groups (14 days: SMD=0.53, 95% CI=0.033-1.02, *P*=0.036; 12 month: SMD=1.03, 95% CI=0.50-1.56, *P*<0.001) (Table 3, Fig. 3).

Table 1. Basic characteristics of eligible studies in our meta-analysis

Author, year	Ethnicity	Case number	Age (y)	Male/female	Genetic equilibrium	Genotype method	Tac measurement method	Time course for Tac measurement	Initial dosage of Tac (mg/kg/d)	ISD therapy
Ferraresso et al, 2007[18]	Caucasian	30	15.8±7	NA	NA	PCR sequencing	EMIT	1, 2, 4, 12, 26, 52 wk	0.3	Tac+steroids+MMF (+induction therapy)
Tirelli et al, 2008[19]	Caucasian	27	13.7	NA	NA	PCR sequencing	EMIT	7, 14, 30, 90, 180, 360 d	0.3	Tac+MMF+steroids (+induction therapy)
Turolo et al, 2010[7]	Caucasian	26	11.6±4.8	NA	Yes	PCR	EMIT	6, 30, 60 d	0.3	CNIs+steroids+MMF
Ferraris et al, 2011[14]	Latino	48	Expresser: 11.6±1.9 Non-expresser: 12.6±0.9	29/19	NA	PCR sequencing	NA	1 y	0.3	CNIs+steroids+MMF
Gijsen et al, 2014[15]	Caucasian	43	11.7±7.4	28/15	Yes	PCR-RFLP	LC-MS	14 d	0.2	Tac+MMF+steroids
Shilbayeh et al, 2013[16]	Asian	38	*CYP3A5*1/*1*: 11.5±2.1 *CYP3A5*1/*3*: 12±2.7 *CYP3A5*3/*3*: 11.2±3.04	17/21	Yes	PCR	EMIT	1, 3, 6, 9, 12 mon	0.3	Tac+MMF+steroids
Lalan et al, 2014[17]	Caucasian	56	13±3.5	NA	Yes	TaqMan	MEIA	12 mon	0.1	Tac+MMF (+steroids)+ induction therapy

Tac: tacrolimus; ISD: immunosuppressive drugs; NA: not available; PCR: polymerase chain reaction; EMIT: enzyme multiplied immunoassay technique; MMF: mycophenolate mofetil; CNIs: calcineurin inhibitors; RFLP: restriction fragment length polymorphism; LC-MS: liquid chromatography-mass spectrometry; MEIA: microparticle enzyme immunoassay.

Table 2. Quality assessment of eligible studies in our meta-analysis

Author, year	Clear statement of background, objectives and hypothesis	Describe the studies information	Clear eligibility criteria	Clear definition of variables	Credible method of concentration measured	Credible genetic testing method	Replicability of statistical methods	Assessment of genetic equilibrium	Sufficient descriptive demographic data	Report the withdrew person and reasons	Statement of outcome data	Funding
Ferraresso et al, 2007[18]	+	+	+	+	+	+	+	-	+	±	+	+
Ferraris et al, 2011[14]	+	+	+	+	+	+	+	-	+	+	+	+
Gijsen et al, 2014[15]	+	+	+	+	+	+	+	+	+	±	+	+
Shilbayeh et al, 2013[16]	+	+	+	+	+	+	+	+	+	±	+	+
Lalan et al, 2014[17]	+	±	-	+	+	+	+	+	+	+	+	+

"+": detailed description; "±": incomplete description; "-": no description.

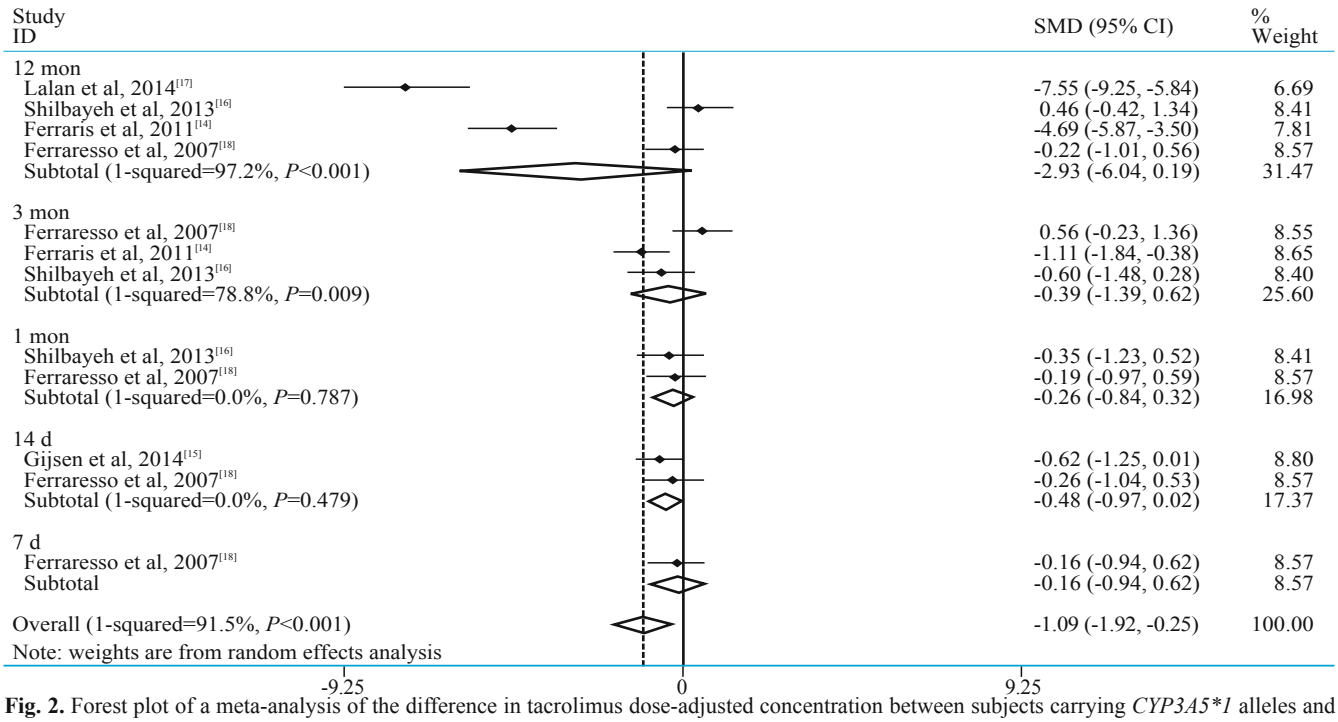

Fig. 2. Forest plot of a meta-analysis of the difference in tacrolimus dose-adjusted concentration between subjects carrying *CYP3A5*1* alleles and those carrying the *CYP3A5*3/*3* genotype. SMD: standard mean difference; CI: confidence interval.

Discussion

Our results provide strong evidence that the loss of function of *CYP3A5*3* variants is associated with increased dose-adjusted C_0 concentrations of tacrolimus and reduced mean daily dose in pediatric RTRs. These data are in accordance with results in adult RTRs.[20]

Evaluation of the association between *CYP3A5* variants and dosage of tacrolimus revealed that *CYP3A5*3/*3* expressers had lower dose requirements than recipients carrying the *CYP3A5*1* variant in pediatric RTRs. Subgroup analyses of different time points after kidney transplantation suggested significant differences in dose requirements of tacrolimus between carriers of *CYP3A5*3/*3* and carriers of *CYP3A5*1* at 14 days and 12 months, respectively, which suggested that at an early stage of two weeks and at long-term stage of relatively stable allograft function, *CYP3A5*1* variant should be considered to administrate more dose of tacrolimus. However, the dosage requirements during the early stage and stable stage still remained unclear. In addition, outcomes of the relationship between *CYP3A5* variants and tacrolimus dose-adjusted C_0 concentrations showed that, at an early stage of

Table 3. Subgroup analysis of *CYP3A5* polymorphisms and pharmacokinetics of tacrolimus

Time course	Studies included	SMD	95% CI	I^2 (%)	Z	*P* value
C_0/dose						
Total	12	-1.09	-1.92, -0.25	91.5	2.55	0.011
7 d	1	-0.16	-0.94, 0.62	-	0.41	0.690
14 d	2	-0.48	-0.97, 0.015	0	1.90	0.0058
1 mon	2	-0.26	-0.85, 0.32	0	0.88	0.380
3 mon	3	-0.39	-1.39, 0.62	78.8	0.76	0.450
12 mon	4	-2.93	-6.04, 0.19	97.2	1.84	0.066
Dose						
Total	11	0.44	0.20, 0.68	85.1	3.58	<0.001
7 d	1	0.16	-0.62, 0.95	-	0.41	0.680
14 d	2	0.53	0.033, 1.02	15.5	2.09	0.036
1 mon	2	0.22	-0.37, 0.80	0	0.73	0.470
3 mon	3	0.17	-0.29, 0.62	75.0	0.71	0.480
12 mon	3	1.03	0.50, 1.56	96.0	3.82	<0.001

SMD: standard mean difference; CI: confidence interval; "-": none.

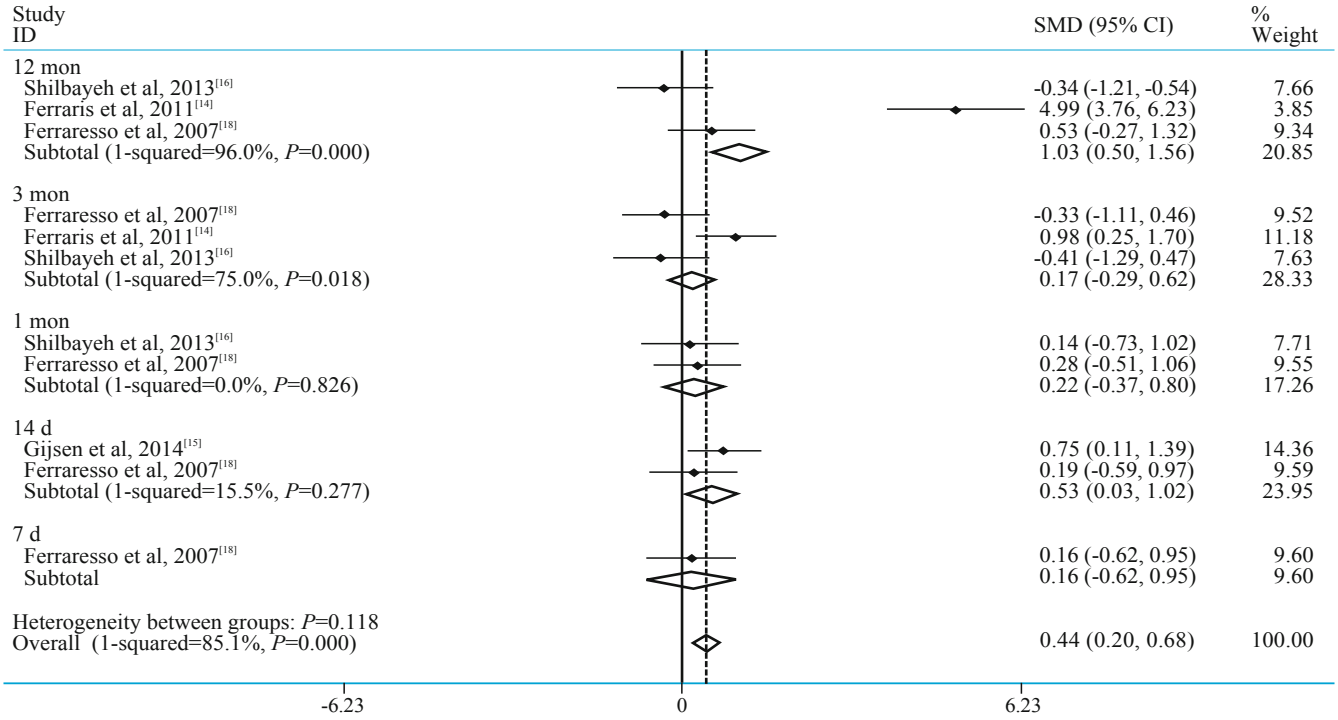

Fig. 3. Forest plot of meta-analysis of the difference in the daily dose requirements of tacrolimus between subjects carrying *CYP3A5*1* alleles and those carrying the *CYP3A5*3/*3* genotype. SMD: standard mean difference; CI: confidence interval.

pediatric kidney transplantation, tacrolimus elimination was slower in recipients carrying the *CYP3A5*3/*3* genotype compared with recipients carrying *CYP3A5*1* variants, corresponding to the results of higher dose requirement for *CYP3A5*1* variants in our analysis.

Defining a safe and effective dose in patients ranging from premature neonates to adolescents is an enormous challenge in kidney transplantation. Evidence suggests that age, sex, body weight, body size, ethnicity, liver/renal function and genotypes contribute to pharmacokinetics in pediatric patients.[21,22] Among pediatric RTRs, age, *CYP3A5* genotype, as well as administration of corticosteroids and azole antifungal agents have been demonstrated to influence the dose-exposure relationship of tacrolimus.[19] In our analysis, we confirmed the contribution of the *CYP3A5* genotype to tacrolimus pharmacokinetics in pediatric RTRs. This contribution could be explained by the truncated protein and inactivated CYP3A5 enzyme coded by the loss-of-function *CYP3A5*3* allele in intron 3 of the *CYP3A5* gene, which replaces the nucleotide A (*CYP3A5*1*) by G (*CYP3A5*3*).[23-26] Moreover, in terms of the daily dose of tacrolimus in pediatric kidney transplantation, Lancia et al[27] suggested that *CYP3A5* expressers require a 1.8-fold higher dose than *CYP3A5* non-expressers, a conclusion that is in accordance with our findings. Therefore, lower doses of tacrolimus would be required for *CYP3A5*3/*3* carriers who metabolize tacrolimus slowly, leading to higher dose-adjusted levels in pediatric kidney transplantation. More importantly, closer TDM is recommended for pediatric RTRs during the change in tacrolimus dose.

Our findings should be interpreted with caution because this meta-analysis had considerable heterogeneity. Subgroup analyses undertaken to explore the source of heterogeneity identified time points to be responsible (at least in part) for the relatively high heterogeneity across eligible studies. However, an analysis of ethnicity, age and publication bias was not carried out, which could have been an origin of considerable heterogeneity among these studies. Furthermore, the uneven results of quality assessment for eligible studies may contribute to the results. As mentioned above, two studies and one study series lacked of the statement or examination of HWE.

In conclusion, our meta-analysis of data on tacrolimus exposure showed that the *CYP3A5*3/*3* genotype has an effect on tacrolimus metabolism in pediatric kidney transplantation, and that *CYP3A5*1* expressers are associated with lower dose-adjusted C_0 concentrations for tacrolimus. Hence, *CYP3A5*1* expressers require a higher daily dose of tacrolimus to achieve the target concentrations compared with non-expressers.

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Ethical approval: The study protocol was in accordance with the ethical standards of the Declarations of Helsinki and Istanbul, approved by the local Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

Competing interest: The authors report no conflicts of interests and have no relevant disclosures.

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