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Genetic polymorphisms of UGT1A8, UGT1A9, UGT2B7 and ABCC2 in Chinese renal transplant recipients and a comparison with other ethnic populations

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Mycophenolate mofetil (MMF), a widely used immunosuppressant, is characterized by highly variable pharmacokinetics. UGT1A8, UGT1A9, UGT2B7 and ABCC2 have been proved to be critical genes associated with inter-individual variation of MMF pharmacokinetics. In this study, we investigated the genetic polymorphisms of UGT1A8*2, UGT1A8*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT1A9 T98C, UGT2B7*2, ABCC2 C-24T and ABCC2 C3972T in 200 Chinese renal transplant recipients and compared them with those in other ethnic groups reported in the literature, to start the exploration of a better use of MMF in Chinese. A much higher frequency of UGT1A8*2 variant allele was found in Chinese than in Caucasians and Africans, while the UGT2B7*2 variant allele was significantly rarer in Chinese than in Caucasians and Africans. For ABCC2, -24T allele was more common and 3972T allele was less common in Chinese than in Caucasians and Africans. However, none of the SNPs in UGT1A9 were present in our study population. The findings of this study suggest that Chinese renal transplant recipients may exhibit a response profile to MMF that is different from those of other ethnic groups.

1. Introduction

Mycophenolate mofetil (MMF) has gained widespread acceptance as the antimetabolite immunosuppressant of choice in solid organ transplant regimens. MMF is the pro-drug of mycophenolic acid (MPA) which is an inhibitor of inosine-5'-monophosphate dehydrogenase. MPA depletes guanosine and deoxyguanosine nucleotides preferentially in T and B lymphocytes, inhibiting proliferation and suppressing cell-mediated immune response and antibody formation (Allison and Eugui 2005).

MPA is metabolized by uridine 5'-diphosphoglucuronosyltransferase (UGTs). This conjugation reaction forms the major phenolic glucuronide metabolite, MPAG, which is an inactive chemical (Schutz et al. 1999). There are also two minor metabolites, acyl-MPAG (AcMPAG) and MPA-phenyl glucoside (Shipkova et al. 1999; Shaw et al. 2003). Of the 19 UGT sequences identified in human, UGT1A8 and UGT1A9 are the primary enzymes participating in the production of MPAG, meanwhile, AcMPAG formation has been ascribed to UGT2B7 (Picard et al. 2005). After these conjugation reactions, MPAG is then excreted into bile, and then de-conjugated back to MPA by gut bacteria (Westley et al. 2006). Biliary secretion of MPAG leading to enterohepatic recirculation (EHC) is considered as a predominant reason of a secondary peak concentration of MPA in plasma. The multidrug resistance-associated protein2 (MRP2, also named ABCC2 or cMOAT, canalicular multispecific organic anion transporter) participates in the enterohepatic recirculation (Kobayashi et al. 2004).

A number of previous studies indicated that genetic polymorphisms of UGT1A8, UGT1A9, UGT2B7 and ABCC2 contribute significantly to inter-patient variability in response to MMF therapy. The clinical impact of UGT 1A9 SNPs on MPA pharmacokinetics have been studied in 95 Caucasian renal transplant recipients (Kuypers et al. 2005). In this research, variant allele carriers of C-2152T and T-275A (or both) had an approximate 50% decreased MPA exposure compared to non-carriers, and MPA $AUC_{0\text{-}12\ h}$ in patients who carried the UGT1A9*3 allele was 85.2% higher than in patients who did not carry the variant allele. Johnson et al. (2008) pointed out that the effect of UGT1A8 genetic polymorphisms on MPA metabolism appears to be modified by concomitant calcineurin inhibitor therapy, and MPA dose-corrected trough concentration were 60% higher in subjects carrying UGT1A8*2 allele than that in subjects did not carry the variant allele in the tacrolimus group. A study enrolling healthy volunteers receiving a single dose of MMF showed that carriers with UGT2B7*2 allele presented significantly higher free MPA C_{max} and elevated free and total MPA

than non-carriers (Levesque et al. 2007). For ABCC2, Naesens et al. (2006) found that carriers of the ABCC C-24T and C3972T variant alleles had higher dose-corrected trough levels (C_0/dose) compared to non-carriers, furthermore, this study suggested that the C-24T SNP was associated with a lower oral clearance of MPA in steady-state conditions.

To date, genetic polymorphisms of UGT1A8, UGT1A9, UGT2B7 and ABCC2 have been studied in Japanese, Korean, Caucasian and African (Saeki et al. 2006; Levesque et al. 2007), while no data are available for the Chinese population. Since ethnicity is an important variable contributing to inter-individual variability in drug metabolism, response and toxicity (Evans et al. 2001), determination of genetic polymorphisms of related drug-metabolizing enzymes and transporters in Chinese renal transplant recipients is necessary for a more efficient use of MMF. In the current study, we investigated the allele frequencies of UGT1A8*2, UGT1A8*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT1A9 T98C, UGT2B7*2, ABCC2 C-24T and ABCC2 C3972T in Chinese renal transplant recipients, and compared the allele frequencies of these SNPs between Chinese and Japanese, Caucasian, African, respectively.

2. Investigations and results

*2.1. Allele frequencies of UGT1A8*2, UGT1A8*3, UGT1A9*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT2B7*2 ABCC2 C-3972T and ABCC2 C-24T in Chinese renal transplant recipients*

The data for UGT1A8*2, UGT1A8*3, UGT1A9*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT2B7*2, ABCC2 C-3972T and ABCC2 C-24T allele frequencies in Chinese renal transplant recipients are listed in Table 1. All SNPs were in Hardy-Weinberg equilibrium. The variant allele frequencies of UGT1A8*2, UGT1A8*3, UGT2B7*2, ABCC2 C -24T and ABCC2 C3972T were 51.0%, 1.0%, 23.8%, 20.3% and 23.0%, respectively, while none of the SNPs in UGT1A9 were present in our study population.

2.2. Comparison of allele frequencies for the eight SNP sites detected in Chinese, Japanese, Caucasian and African populations

As shown in Table 2, the variant frequency of UGT1A8*2 in Chinese was slightly lower than that in Japanese (Saeki et al. 2006), but significantly higher than those in Caucasians and Africans (Levesque et al. 2007). No significant differences of UGT1A8*3 variant frequencies were found between Chinese and other ethnic populations (Saeki et al. 2006; Levesque et al. 2007; Sai et al. 2008). For the three SNPs in UGT1A9, all of them were detected in Caucasians with low frequencies (5.9, 6.1 and 2.2% for C-2152T, T-275A and T98C(*3), respectively) (Villeneuve et al. 2003; Levesque et al. 2007), T-275A was observed in Africans with a frequency of 4.2%. However, none of them was present in our study population, Japanese and South-East Asians (Saeki et al. 2006). The variant frequencies of UGT2B7*2 were significantly higher in Caucasians and Africans (Mehlotra et al. 2007) than that in Chinese, while no significant difference were found between the Chinese and Japanese (Saeki et al. 2006).

The variant frequency of the known common SNP ABCC2 C-24T in this study was higher than that in Africans but not different from those in Caucasians and Japanese (de Jong et al. 2007; Sai et al. 2008). The variant frequency of another common SNP, ABCC2 C3972T in Chinese was lower than those in Caucasians and Africans while a little bit higher than that in Japanese (de Jong et al. 2007; Sai et al. 2008).

3. Discussion

We investigated the frequencies of several important SNPs in UGT1A8, UGT1A9, UGT2B7 and ABCC2 in Chinese renal transplant recipients. To our knowledge, this is the first report to describe the genetic polymorphisms of UGT1A8, UGT1A9, UGT2B7 and ABCC2 in a Chinese population.

The results of the current study provided evidence that allele frequencies of the eight SNPs in Chinese were markedly different from those of Caucasians and Africans, which is accordant to

Table 1: Frequencies of UGT1A8, UGT1A9, UGT2B7 and ABCC2 polymorphisms in 200 renal transplant recipients

Gene	SNP	Genotype	n	Genotype frequency (%)	Allele	Allele frequency (%)
UGT1A8	C518G(*2)	C/C	42	21.0	C	49.0
		C/G	112	56.0	G	51.0
		G/G	46	23.0		
	G830A(*3)	G/G	196	98.0	G	99.0
		G/A	4	2.0	A	1.0
		A/A	0	0		
UGT1A9	C-2152T	C/C	200	100	C	100
		C/T	0	0	T	0
		T/T	0	0		
	T-275A	T/T	200	100	T	100
		T/A	3	0	A	0
		A/A	0	0		
	T98C(*3)	T/T	200	100	T	100
		T/C	0	0	C	0
		C/C	0	0		
UGT2B7	C802T(*2)	C/C	120	60.0	C	76.2
		C/T	65	32.5	T	23.8
		T/T	15	7.5		
ABCC2	C-24T	C/C	130	65.0	C	79.7
		C/T	59	29.5	T	20.3
		T/T	11	5.5		
	C3972T	C/C	123	61.5	C	77.0
		C/T	62	31.0	T	23.0
		T/T	15	7.5		

Table 2: Comparison of allele frequencies for eight SNP sites detected in Chinese and other ethnic groups

SNPs	Allele	Allele frequency							
		Chinese in this study		Japanese		Caucasian		American African	
		n	Frequency (%)	n	Frequency (%)	n	Frequency (%)	n	Frequency (%)
UGT1A8	C	400	49.0	602[a]	40.0*	610[b]	76.7[#]	88[c]	92.1[§]
C518G(*2)	G		51.0		60.0		23.3		7. 9
UGT1A8	G	400	99.0	602[a]	99.0	610[b]	98.7	48[d]	100.0[§]
G830A(*3)	A		1.0		1.0		1.3		0
UGT1A9	C	400	100.0	602[a]	100.0	610[b]	94.1[#]		ND
C-2152T	T		0		0		5.9		ND
UGT1A9	T	400	100.0	602[a]	100.0	610[b]	93.9[#]	48[e]	95.8[§]
T-275A	A		0		0		6.1		4.2
UGT1A9	T	400	100.0	602[a]	100.0	402[f]	98.8[#]	40[f]	100.0
T98C(*3)	C		0		0		1.2		0
UGT2B7	C	400	76.2	320[g]	75.6	188[h]	48.0[#]	86[h]	66.0
C802T(*2)	T		23.8		24.4		52.0		34.0
ABCC2	C	400	79.7	472[i]	82.6	334[j]	85.0	200[k]	94.0[§]
C-24T	T		20.3		17.4		15.0		6.0
ABCC2	C	400	77.0	472[i]	78.4	334[j]	68.0[#]	194[k]	72.7[§]
C3972T	T		23.0		21.6		32.0		27.3

ND, not determined

$P < 0.05$, Chinese vs. Japanese. # $P < 0.05$, Chinese vs. Caucasian[§] $P < 0.05$, Chinese vs. African

[a] Saeki et al. (2006)

[b] Levesque et al. (2007)

[c] http://www.pharmgkb.org/views/reports/loadFrequencyInSampleSets.action?varRptId = 136451559&submissionId = PS206119

[d] Sai et al. (2008)

[e] http://www.pharmgkb.org/views/reports/loadFrequencyInSampleSets.action?varRptId = 125860516&submissionId = PS205164

[f] Villeneuve et al. (2003)

[g] Saito et al. (2006); Sai et al. (2008)

[h] Mehlotra et al. (2007)

[i] Sai et al. (2008)

[j] de Jong et al. (2007)

[k] http://www.pharmgkb.org/views/reports/loadFrequencyInSampleSets.action?varRptId = 516678576&submissionId = PS203864a

the results of previous reports in other Asian populations (Ito et al. 2001; Choi et al. 2007). Such marked inter-ethnic differences suggesting that Chinese renal transplant recipients may exhibit a response profile to MMF that is different from those of other ethnic groups.

In this study, no subjects with UGT1A9*3, UGT1A9 C-2152T and UGT1A9 T-275A variant alleles were found among 200 Chinese renal transplant recipients, which is in agreement with those data reported of Japanese and South-East Asian (Saeki et al. 2006), suggesting that the three SNPs in UGT1A9 detected in this study are absent or at least very rare in the Chinese, Japanese and South-East Asian populations, additionally, the polymorphism UGT1A8*3, presents so as little as 1% in our study population. These rare SNPs may be lacking of clinical significance of guiding individualized MMF dosing in Chinese renal transplant recipients.

According to the previous study, variant alleles of UGT1A8*2, UGT2B7*2, ABCC2 C-24T and ABCC2 C3972T were found to be correlated with higher MPA exposure (Naesens et al. 2006; Levesque et al. 2007; Johnson et al. 2008). Significantly higher variant frequency of UGT1A8*2 and relatively higher variant frequency of ABCC2 C-24T suggesting that Chinese may benefit more from a lower MMF dose than Caucasians and Africans, while significantly lower variant frequency of UGT2B7*2 and relatively lower variant frequency of ABCC2 C3972T suggesting Chinese may suffer from less susceptibility to MMF and higher doses are needed compared to Caucasians and Africans. The combined effects of these SNPs on MMF pharmacokinetics have not yet been demonstrated in Chinese population and need further study.

In conclusion, in this study, we demonstrate the genetic polymorphisms of UGT1A8, UGT1A9, UGT2B7 and ABCC2 in Chinese renal transplant recipients. The results of these SNPs frequencies are comparable to other Asian populations, but different from those in Caucasians and Africans. Further studies are needed to investigate the effects of these SNPs on MMF pharmacokinetics in Chinese renal transplant recipients. Ongoing investigations will hopefully be helpful in providing a scientific basis for optimization of MMF pharmacotherapy in Chinese renal transplant recipients.

4. Experimental

4.1. Chemicals and reagents

Restriction enzymes were purchased at New England Biolabs (Beverly, MA) or Takara Bio (Shiga, Japan). The ExTaq kit was from Takara Bio. The water used was of Milli-Q grade purified by a Milli-A UV Purification System (Millipore, Bedford, MA, USA). All other chemicals and reagents were of analytical or HPLC grade as appropriate.

4.2. Study population

200 Chinese renal allograft recipients (156 male and 44 female, mean age = 38.19 ± 12.83 years with a range of 18 to 70 years), who received renal transplantation between 2005 and 2008 at the Kidney Transplant Department, Transplant Center, the First Affiliated Hospital, Sun Yat-sen University and received maintenance treatment with MMF afterwards, were enrolled in this study. The ethics approval of this study was obtained from the ethics committee of the First Affiliated Hospital of Sun Yat-sen University, and written informed consent was obtained from all participants.

4.3. DNA extraction

Total genomic DNA was extracted from peripheral leukocytes by the phenol-chloroform extraction method (Chomczynski and Sacchi 1987). The DNA concentration was measured using the GeneQuant photometer (Amersham Biosciences Inc., Piscataway, NJ). The purity of DNA was 99.5%.

Table 3: Polymerase chain reaction-restriction fragment length polymorphism genotyping

SNP	Primer sequence	Amplicon size (bp)	Restriction enzyme
UGT1A8	F: CAG TTC TCT CAT GGC TCG CA	750	*Alu I*
C518G(*2)	R: GTG TGG CTG TAG AGA TCA TAT GCT		
UGT1A8	F: TCT TCA TTG GTG GTA TCA GCT	215	*Pvu II*
G830A(*3)	R: AAA ATT TGA TAA CTG ATG AGT ACA TA		
UGT1A9	F: TTG AGA CAG AGT CGT GCT GTT T	198	*Mse I*
C-2152T	R:AGG TCA AGG TGG GCG TAT C		
UGT1A9	F: TCA GTG CTA AGG GCC TTG TT	250	*Xba I*
C-275T	R: CCT GTG CTG CAA TGT TAA GTC TA		
UGT1A9	F: GTC TCT GAT GGC TTG CAC A	226	*Sty I*
T98C(*3)	R: ATC CCC CCT GAG AAT GAG TT		
UGT2B7	F: GAC AAT GGG GAA AGC TGA CG	116	*Fok I*
C802T(*2)	R: GTT TGG CAG GTT TGC AGT G		
ABCC2	F: AAC TTA CTT CTC ATC TTG TCT CCT TGC	220	*Cla I*
C-3972T	R: CTC CAC CTA CCT TCT CCA TGC TAT C		
ABCC2	F: CTG TTC CAC TTT CTT TGA TGA	185	*Bbs I*
C-24T	R: TCT TGT TGG TGA CCA CCC TAA		

4.4. Genotyping

All patients were genotyped for the UGT1A8*2, UGT1A8*3, UGT1A9*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT2B7*2 ABCC2 C-24T and ABCC2 C-3972T, by using published polymerase chain reaction–restriction fragment length polymorphism methods (PCR-RFLP) (Holthe et al. 2002; van der Logt et al. 2004; Kuypers et al. 2005; Naesens et al. 2006) with minor modifications. PCR amplification was carried out in a total reaction volume of 25 μl containing 50 ng genomic DNA, 2 μl dNTPs (0.25 mmol/l), 1 μ1 each of primer (10 μl mol/l), 2.5 μl 10 × Ex Taq buffer (Mg2+ Plus), 0.75 U Ex Taq DNA polymerase. The PCR conditions for UGT1A9*3, UGT1A9 C-2152T, UGT1A9 T-275A, UGT2B7*2, ABCC2 C-3972T and C-24T were 5 min at 95 °C, then 30 cycles of 30 s at 95 °C, 30 s at 55–65 °C, and 30 s at 72 °C, followed by a final extension at 72 °C for 5 min. The PCR conditions for UGT1A8*2 and UGT1A8*3 were 5 min at 95 °C, the 30 cycles of 30 s at 95 °C, 1 min at 49–65 °C, and 1 min at 72 °C, followed by a final extension at 72 °C for 7 min. After amplification, the PCR products were digested with the restriction enzymes and analyzed after gel electrophoresis. Details regarding the primer sequences, amplicon sizes and restriction enzymes used are shown in Table 3. Correctness of genotyping was confirmed by DNA sequencing for two cases of each genotype.

4.5. Statistical analysis

Statistical analyses were performed with SPSS 16.0 software (SPSS, Chicago, USA). Deviation from the Hardy-Weinberg equilibrium of genotype frequency was evaluated with the χ^2 test. Differences in the allele frequencies between different ethnic groups were measured using the χ^2 test or Fisher's exact test. A $P < 0.05$ was considered statistically significant.

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References

Allison AC, Eugui EM (2005) Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. Transplantation 80: S181–190.

Choi JH, Ahn BM, Yi J, Lee JH, Lee JH, Nam SW, Chon CY, Han KH, Ahn SH, Jang IJ, Cho JY, Suh Y, Cho MO, Lee JE, Kim KH, Lee MG (2007) MRP2 haplotypes confer differential susceptibility to toxic liver injury. Pharmacogenet Genomics 17: 403–415.

Chomczynski P, Sacchi N (1987) Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. Anal Biochem 162: 156–159.

de Jong FA, Scott-Horton TJ, Kroetz DL, McLeod HL, Friberg LE, Mathijssen RH, Verweij J, Marsh S, Sparreboom A (2007) Irinotecan-induced diarrhea: functional significance of the polymorphic ABCC2 transporter protein. Clin Pharmacol Ther 81: 42–49.

Evans DA, McLeod HL, Pritchard S, Tariq M, Mobarek A (2001) Interethnic variability in human drug responses. Drug Metab Dispos 29: 606–610.

Holthe M, Klepstad P, Zahlsen K, Borchgrevink PC, Hagen L, Dale O, Kaasa S, Krokan HE, Skorpen F (2002) Morphine glucuronide-to-morphine plasma ratios are unaffected by the UGT2B7 H268Y and UGT1A1*28 polymorphisms in cancer patients on chronic morphine therapy. Eur J Clin Pharmacol 58: 353–356.

Ito S, Ieiri I, Tanabe M, Suzuki A, Higuchi S, Otsubo K (2001) Polymorphism of the ABC transporter genes, MDR1, MRP1 and MRP2/cMOAT, in healthy Japanese subjects. Pharmacogenetics 11: 175–184.

Johnson LA, Oetting WS, Basu S, Prausa S, Matas A, Jacobson PA (2008) Pharmacogenetic effect of the UGT polymorphisms on mycophenolate is modified by calcineurin inhibitors. Eur J Clin Pharmacol 64: 1047–1056.

Kobayashi M, Saitoh H, Kobayashi M, Tadano K, Takahashi Y, Hirano T (2004) Cyclosporin A, but not tacrolimus, inhibits the biliary excretion of mycophenolic acid glucuronide possibly mediated by multidrug resistance-associated protein 2 in rats. J Pharmacol Exp Ther 309: 1029–1035.

Kuypers DR, Naesens M, Vermeire S, Vanrenterghem Y (2005) The impact of uridine diphosphate-glucuronosyltransferase 1A9 (UGT1A9) gene promoter region single-nucleotide polymorphisms T-275A and C-2152T on early mycophenolic acid dose-interval exposure in de novo renal allograft recipients. Clin Pharmacol Ther 78: 351–361.

Levesque E, Delage R, Benoit-Biancamano MO, Caron P, Bernard O, Couture F, Guillemette C (2007) The impact of UGT1A8, UGT1A9, and UGT2B7 genetic polymorphisms on the pharmacokinetic profile of mycophenolic acid after a single oral dose in healthy volunteers. Clin Pharmacol Ther 81: 392–400.

Mehlotra RK, Bockarie MJ, Zimmerman PA (2007) Prevalence of UGT1A9 and UGT2B7 nonsynonymous single nucleotide polymorphisms in West African, Papua New Guinean, and North American populations. Eur J Clin Pharmacol 63: 1–8.

Naesens M, Kuypers DR, Verbeke K, Vanrenterghem Y (2006) Multidrug resistance protein 2 genetic polymorphisms influence mycophenolic acid exposure in renal allograft recipients. Transplantation 82: 1074–1084.

Picard N, Ratanasavanh D, Premaud A, Le Meur Y, Marquet P (2005) Identification of the UDP-glucuronosyltransferase isoforms involved in mycophenolic acid phase II metabolism. Drug Metab Dispos 33: 139–146.

Saeki M, Saito Y, Jinno H, Sai K, Ozawa S, Kurose K, Kaniwa N, Komamura K, Kotake T, Morishita H, Kamakura S, Kitakaze M, Tomoike H, Shirao K, Tamura T, Yamamoto N, Kunitoh H, Hamaguchi T, Yoshida T, Kubota K, Ohtsu A, Muto M, Minami H, Saijo N, Kamatani N, Sawada JI (2006) Haplotype structures of the UGT1A gene complex in a Japanese population. Pharmacogenomics J 6: 63–75.

Sai K, Saito Y, Itoda M, Fukushima-Uesaka H, Nishimaki-Mogami T, Ozawa S, Maekawa K, Kurose K, Kaniwa N, Kawamoto M, Kamatani N, Shirao K, Hamaguchi T, Yamamoto N, Kunitoh H, Ohe Y, Yamada Y, Tamura T, Yoshida T, Minami H, Matsumura Y, Ohtsu A, Saijo N, Sawada J (2008) Genetic variations and haplotypes of ABCC2 encoding MRP2 in a Japanese population. Drug Metab Pharmacokinet 23: 139–147.

Saito K, Moriya H, Sawaguchi T, Hayakawa T, Nakahara S, Goto A, Arimura Y, Imai K, Kurosawa N, Owada E, Miyamoto A (2006) Haplotype analysis of UDP-glucuronocyltransferase 2B7 gene (UGT2B7) polymorphisms in healthy Japanese subjects. Clin Biochem 39: 303–308.

Schutz E, Shipkova M, Armstrong VW, Wieland E, Oellerich M (1999) Identification of a pharmacologically active metabolite of mycophenolic acid in plasma of transplant recipients treated with mycophenolate mofetil. Clin Chem 45: 419–422.

Shaw LM, Korecka M, Venkataramanan R, Goldberg L, Bloom R, Brayman KL (2003) Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. Am J Transplant 3: 534–542.

Shipkova M, Armstrong VW, Wieland E, Niedmann PD, Schutz E, Brenner-Weiss G, Voihsel M, Braun F, Oellerich M (1999) Identification of glucoside and carboxyl-linked glucuronide conjugates of mycophenolic acid in plasma of transplant recipients treated with mycophenolate mofetil. Br J Pharmacol 126: 1075–1082.

van der Logt EM, Bergevoet SM, Roelofs HM, van Hooijdonk Z, te Morsche RH, Wobbes T, de Kok JB, Nagengast FM, Peters WH (2004) Genetic polymorphisms in UDP-glucuronosyltransferases and glutathione S-transferases and colorectal cancer risk. Carcinogenesis 25: 2407–2415.

Villeneuve L, Girard H, Fortier LC, Gagne JF, Guillemette C (2003) Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anticancer drugs. J Pharmacol Exp Ther 307: 117–128.

Westley IS, Brogan LR, Morris RG, Evans AM, Sallustio BC (2006) Role of Mrp2 in the hepatic disposition of mycophenolic acid and its glucuronide metabolites: effect of cyclosporine. Drug Metab Dispos 34: 261–266.