Chulalongkorn Medical Journal

Volume 57
Issue 1 *January 2013*

Article 5

1-1-2013

Prevalence of UGT1A4 and UGT2B7 polymorphismsin Thai patients

N Singkham

S Towanabut

S Lertkachatarn

B. Punyawudho

Chula Med J Vol. 57 No. 1 January-February 2013

Prevalence of *UGT1A4* and *UGT2B7* polymorphisms in Thai patients

Noppaket Singkham* Somchai Towanabut**
Surang Lertkachatarn** Baralee Punyawudho*

Singkham N, Towanabut S, Lertkachatarn S, Punyawudho B. Prevalence of *UGT1A4* and *UGT2B7* polymorphisms in Thai patients. Chula Med J 2013 Jan - Feb; 57(1): 49 - 60

Background : *UGT1A4 and UGT2B7 play an important role in the metabolism of several endogenous substrates and xenobiotics including clozapine, morphine and lamotrigine. The polymorphisms of UGT1A4 and UGT2B7 may be associated with the variability of glucuronidation activity which leads to the interindividual variability of lamotrigine concentrations among patients. Even though, there is an evidence of the variation of UGT polymorphisms between races, the information of UGT polymorphisms in Thai population is limited.*

Objective : *To investigate the frequencies of UGT1A4 and UGT2B7 polymorphisms in Thai patients.*

Setting : *Prasat Neurological Institute, Bangkok.*

Research design : *Prospective descriptive study.*

Patients : *Patients with epilepsy and psychiatric disorder were included.*

Methods : *Four single nucleotide polymorphisms, UGT1A4 142T>G, UGT1A4 70C>T, UGT2B7 372A>G, and UGT2B7 -161C>T were identified. Genotyping was carried out by Taqman allelic discrimination assays using Taqman probes. Chi-square tests were used to assess*

* Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University

** Prasat Neurological Institute, Bangkok, Thailand.

the distribution of the observed genotypes according to Hardy-Weinberg equilibrium and to compare the allele frequencies between the Thais and other populations.

Results : *There were 81 patients included in this study. The allele frequencies of UGT1A4 142T>G, UGT2B7 372A>G and UGT2B7 -161C>T were 27%, 20%, and 25%, respectively. The polymorphism of UGT1A4 70C>T was not detected in this population.*

Conclusion : *Nearly half of the patients are wild-type of UGT1A4 142T>G, UGT2B7 372A>G and UGT2B7 -161C>T. The allele frequencies of UGT1A4 70C>T, UGT2B7 372A>G, and UGT2B7 -161C>T are similar to the values previously reported in other Asian populations, but the frequency of UGT1A4 142T>G in this Thai population is higher than those of other Asian populations. Our findings provide initial information for designing studies for investigating the association between genetic factors and pharmacokinetics of these UGTs substrates.*

Keywords : *UGT1A4, UGT2B7, polymorphisms, Thai.*

Reprint request : Punyawudho B. Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.
E-mail address: Baralee.P@chula.ac.th

Received for publication. January 3, 2012.

นภเกตน์ สิงห์คำ, สมชาย โตวณะบุตร, สุรางค์ เลิศคชาธาร, บราลี ปัญญาวุธโธ. ความชุกของภาวะพหุสัณฐานของยีน *UGT1A4* และ *UGT2B7* ในผู้ป่วยชาวไทย. จุฬาลงกรณ์เวชสาร 2556 ม.ค. – ก.พ.;57(1): 49 – 60

เหตุผลของการทำวิจัย : *UGT1A4 และ UGT2B7 เป็นเอนไซม์ที่มีบทบาทในการเปลี่ยนแปลงสารหลายชนิดภายในและสิ่งแปลกปลอมจากภายนอกร่างกาย รวมทั้งยาโคลซาปีน มอร์ฟีน และลาโมทริจีน หากมีการกลายพันธุ์ของยีนที่ควบคุมการทำงานของเอนไซม์อาจมีผลต่อการเมตาบอลิซึมยาซึ่งนำไปสู่ความผันแปรของระดับยาในเลือดของผู้ป่วยแต่ละราย มีหลักฐานพบความผันแปรทางพันธุกรรมของยีนที่มีความแตกต่างระหว่างเชื้อชาติ แต่ยังไม่พบการศึกษาภาวะพหุสัณฐานของยีน UGT1A4 และ UGT2B7 ในประชากรไทย*

วัตถุประสงค์ : *ศึกษาความชุกของภาวะพหุสัณฐานของยีน UGT1A4 และ UGT2B7 ในผู้ป่วย ชาวไทย*

รูปแบบการวิจัย : *การศึกษาเชิงพรรณนาแบบไปข้างหน้า*

สถานที่ที่ทำการศึกษา : *สถาบันประสาทวิทยา*

ผู้ป่วยที่ได้ทำการศึกษา : *ผู้ป่วยที่เข้ารับการรักษาในคลินิกโรคลมชักและคลินิกจิตเวช*

วิธีการศึกษา : *ตรวจภาวะพหุสัณฐานของยีน UGT1A4 142 T>G, UGT1A4 70 C>T (P24T), UGT2B7 372 A>G และ UGT2B7 -161C>T ด้วยวิธี Taqman allelic discrimination assay ใช้สถิติไคว์สแคว์เพื่อทดสอบการกระจายตัวของจีโนไทป์ตามกฎของ Hardy–Weinberg Equilibrium และเปรียบเทียบความถี่ของอัลลีลของยีนระหว่างประชากรไทยและเชื้อชาติอื่น*

ผลการศึกษา : *ในผู้ป่วย 81 ราย พบว่าความถี่ของอัลลีล UGT1A4 142T>G, UGT2B7 372A>G และ UGT2B7 -161C>T เป็น 27%, 20% และ 25% ตามลำดับ แต่ไม่พบภาวะพหุสัณฐานของยีน UGT1A4 70 >T ในผู้ป่วยชาวไทย*

วิจารณ์และสรุป : *ยีน UGT1A4 142T>G, UGT2B7 372A>G และ UGT2B7 -161C>T ในผู้ป่วยชาวไทยส่วนใหญ่มีลักษณะเป็น wild-type โดยความถี่ของอัลลีลของยีน UGT1A4 70C>T, UGT2B7 372A>G และ UGT2B7 -161C>T มีความคล้ายคลึงกับประชากรเอเชียอื่น ๆ แต่พบว่ายีน UGT1A4 142T>G ในประชากรไทยมีความถี่ของอัลลีลสูงกว่าประชากรเอเชียอื่น ๆ ผลการศึกษานี้สามารถนำไปใช้เป็นข้อมูลเบื้องต้นในการศึกษาความสัมพันธ์ระหว่างความผันแปรทางพันธุกรรมของยีน UGT1A4 และ UGT2B7 และเภสัชจลนศาสตร์ของสารตั้งต้นที่ถูกเมตาบอไลซ์ ด้วยเอนไซม์เหล่านี้*

คำสำคัญ : *UGT1A4, UGT2B7, ภาวะพหุสัณฐานของยีน, ประชากรไทย.*

Currently, individualization of drug therapy to obtain better responses while decreasing the adverse effects, has earned more attention. Drug responses largely depend on several factors such as patient characteristics, co-medications, pathophysiology, and genetics.[1-2] Genetic variation plays a pivotal role in the difference of drug concentrations, responses, and safety. It is postulated that genetic difference accounts for 20 - 95% of the interindividual variability in drug responses.[3] Therefore, pharmacogenetics is one of the important tools to be used for drug individualization.[1-3] There have been a number of the studies investigating the pharmacogenetics of Phase I enzymes. However, the information of genetic variation in Phase II enzymes is scarce.[2, 4]

Uridine-diphosphate glucuronosyltransferases (UGTs) are Phase II enzymes responsible for the metabolism of several xenobiotics and endobiotics. In human, UGT enzymes have been classified into two primary families, UGT1 and UGT2, according to their amino acid sequences.[5-6] UGT1A4 is a primary human UGT isoform that catalyzes many therapeutic agents including clozapine, tamoxifen and lamotrigine.[4-5] UGT2B7 is an important enzyme responsible for catalyzing a wide range of xenobiotic substances such as polycyclic aromatic hydrocarbon, valproic acid, and may involve in the metabolism of lamotrigine.[4-5, 7]

Recent studies have discovered numerous variations of *UGT1A4*.[5] Two common polymorphisms were founded in exon 1. One is the transversion of T to G at nucleotide position 142, resulting in an amino acid change from leucine (L) to valine (V), *UGT1A4* 142T>G (L48V). The other is the transversion of C to T at nucleotide position 70, resulting in amino acid change from praline to threonine; *UGT1A4* 70C>T (P24T). The *UGT1A4* 142T>G (L48V) and *UGT1A4* 70C>T (P24T) were first detected in German population.[8] These two polymorphisms have also been reported in other Caucasians such as Turkish and Swedish populations.[9-10] In Asian populations, the polymorphism of *UGT1A4* 142T>G (L48V) has been identified in Japanese and Korean populations, whereas the polymorphism of *UGT1A4* 70C>T (P24T) was not found.[11-13]

UGT2B7 is involved in a glucuronidation of several drugs such as morphine, valproic acid, and lamotrigine.[5, 7] Several polymorphisms of *UGT2B7* have been reported in Asian and Caucasian populations.[14-20] *UGT2B7* -161C>T has been identified within the promoter region that was found to be in complete linkage disequilibrium with *UGT2B7* 802T>C (H268Y). This variation does not change the amino acid of *UGT2B7* but may affect the level of transcription of this enzyme.[18] Another polymorphism of *UGT2B7* commonly found is 372A>G which is a transversion at nucleotide position 372. This variation was found in exon1.[16] However, there are few studies that investigated the function of this variation.

Although the variant alleles of *UGT1A4* and *UGT2B7* have been described in many ethnicities, there is no study that investigates genetic polymorphisms of *UGT1A4* and *UGT2B7* in Thai population. Therefore, the purpose of this study was to investigate the frequencies of *UGT1A4* and *UGT2B7* in Thai patients.

Patients and Methods

Patients

A total of 81 Thai patients with epilepsy and

psychiatric disorder were recruited from Prasat Neurological Institute during 10 January to 30 July 2011. The study protocol has been approved by the ethics committee of Prasat Neurological Institute, and informed consent was obtained from all patients.

Human genomic DNA samples

Five milliliters of whole blood from each patient was collected in EDTA tubes. Blood samples were centrifuged at 2500 g for 10 minutes at room temperature to obtain buffy coat. Two hundred microliters of buffy coat was transferred into 1.5 mL microcentrifuge tube, and then frozen at -20 ^{o}C until DNA extraction. DNA purification was carried out by QIAamp® DNA Blood Mini kit (Qiagen, Hilden, Germany) according to the manufacturer instruction.

Genotyping Analysis

Four single nucleotide polymorphisms (SNPs) including *UGT1A4* 142T>G (L48V), *UGT1A4* 70C>T (P24T), *UGT2B7* 372A>G (R124R), and *UGT2B7* -161C>T were investigated. The SNPs detection was carried out by Taqman allelic discrimination assays with fluorogenic probes (Applied Biosystems, Foster City, CA). The probe for all 4 SNPs were designed by Applied Biosystems and are presented in Table 1. All reactions were analyzed by Applied Biosystems 7500 Real-Time PCR System.

Statistical analysis

All the observed polymorphisms were presented as frequencies. The genotypes were characterized as wild-type (two copies of the common alleles), heterozygous (one copy of the variant allele), and homozygous (two copies of the variant alleles). The distribution of observed genotypes according to Hardy-Weinberg equilibrium ($p^2 + 2pq + q^2 = 1$; where p and q are the frequencies of the alleles) was tested by Chi-square test.[21] The comparisons of the allele frequencies between different populations were determined by Chi-square test. Statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS version 17, SPSS Co., Ltd., Bangkok Thailand) software. The level of significance was set at 0.05.

Table 1. Information of the allele probes for the detection of *UGT1A4* and *UGT2B7* polymorphisms.

SNPs (rs number)	**Probes**	**Sequence of allele probes**
UGT1A4 142T>G	Allele 1	CCCTGGCTCAGCATGCGGGAGGCC**G**TGCGGGAGCTCCATGCCAGAGGCCA
(rs2011425)	Allele 2	CCCTGGCTCAGCATGCGGGAGGCC**T**TGCGGGAGCTCCATGCCAGAGGCCA
UGT1A4 70C>T	Allele 1	ACTGCTGCTCCTCCTCAGTGTCCAG**A**CCTGGGCTGAGAGTGGAAAGGTGTT
(rs6755571)	Allele 2	ACTGCTGCTCCTCCTCAGTGTCCAG**C**CCTGGGCTGAGAGTGGAAAGGTGTT
UGT2B7 372A>G	Allele 1	TGTCAATATTTGGTGACATAACTAG**A**AAGTTCTGTAAAGATGTAGTTTCAA
(rs2836506)	Allele 2	TGTCAATATTTGGTGACATAACTAG**G**AAGTTCTGTAAAGATGTAGTTTCAA
UGT2B7 -161C>T	Allele 1	CAGATCATTTACCTTCATTTGTCTC**C**TTGCCATCCACATGCTCAGACTGTT
(rs7668258)	Allele 2	CAGATCATTTACCTTCATTTGTCTC**T**TTGCCATCCACATGCTCAGACTGTT

rs number: reference single nucleotide polymorphisms number

probe: a fragment of DNA which is used to detect the presence of nucleotide sequences

Results

A total of 81 patients were enrolled in this study. There were 47 females (58%) and 34 males (42%). The mean age was 47.68 ± 15.22 years old. Summary of demographic data are presented in Table 2

This study found that the frequencies of the wild-type of *UGT1A4* 142T>G, *UGT2B7* 372A>G and *UGT2B7* -161C>T were 54%, 63%, and 55% respectively. The frequencies of the homozygous genotype of *UGT1A4* 142T>G, *UGT2B7* 372A>G and *UGT2B7* -161C>T were 7%, 2%, and 5% respectively. However, the variant of *UGT1A4* 70C>T was not found in this Thai population. All allele SNPs were in the Hardy Weinberg equilibrium *(P >0.05)*. Genotyping data from a total of 81 Thai patients are shown in Table 3.

Table 2. Demographic data of patients who enrolled the study (n = 81 patients).

Characteristics	Frequency, (mean ± SD)	% (range)
Gender (female/male)	47/34	58/42
Age (years)	(47.68 ± 15.22)	(18 - 82)
Underlying disease		
Epilepsy	33	40.74
Psychiatric disorder	47	58.02
Neuropathic pain	1	1.23

Table 3. Genotype frequencies of *UGT1A4* and *UGT2B7* in Thai patients (*n* = 81 patients).

Polymorphisms	Genotype	Frequency	%	*P* value*
UGT1A4 142T>G	TT	44	54	*P* = 0.973
	TG	31	38	
	GG	6	7	
UGT1A4 70C>T	CC	81	100	
	CT	0	0	
	TT	0	0	
UGT2B7 372A>G	AA	51	63	*P* = 0.776
	AG	28	35	
	GG	2	2	
UGT2B7 -161C>T	CC	45	55	*P* = 0.837
	CT	32	40	
	TT	4	5	

*Chi-square test, Hardy-Weinberg equilibrium

In this study, the allele frequencies of *UGT1A4* 142T>G, *UGT2B7* 372A>G and *UGT2B7* -161C>T were 27%, 20% and 25%, respectively. The comparison of *UGT1A4* and *UGT2B7* allele frequencies between this study population and other populations from previous ones are shown in Table 4. Allelic frequency of *UGT1A4* 142T>G in this study was significantly different from that of the Caucasian populations including the German and the Swedish *(P <0.001)*.[8, 10] However, it was similar to the frequency obtained from Turkish population *(P = 0.367)*.[9] When compared with other Asian populations, the allelic frequency of *UGT1A4* 142T>G in this study was significantly different from that of the Japanese and Korean populations.[11-13] The results from this study showed no polymorphisms of *UGT1A4* 70C>T in Thai population that was similar to a previous study in Japanese populations. [12-13]

Table 4. Comparison of *UGT1A4* and *UGT2B7* allele frequencies among different populations.

Polymorphism	Ethnicity	Number of subject	% allele frequency		p-value*
UGT1A4 142T>G			T	G	
	Thai (this study)	81	73	27	
	Japanese[12]	256	87.11	12.89	<0.001
	Japanese[13]	100	83.5	16.5	0.014
	Korean[11]	40	85	15	0.035
	Germany[8]	316	91	9	<0.001
	Turkish[9]	129	76.74	23.26	0.367
	Swedish[10]	112	87.05	12.95	<0.001
UGT1A4 70C>T			C	T	
	Thai (this study)	81	100	0	
	Japanese[12]	256	100	0	
	Japanese[13]	100	100	0	
	German[8]	318	92	8	<0.001
	Turkish[9]	129	96.2	3.8	0.011
UGT2B7 372A>G			A	G	
	Thai (this study)	81	80	20	
	Japanese[14]	136	80.1	19.9	0.98
	Japanese[16]	46	77.2	22.8	0.562
	Korean[17]	50	87	13	0.159
	Spain[20]	53	79.25	20.75	0.842

*Chi-square test

Table 4. (cont) Comparison of *UGT1A4* and *UGT2B7* allele frequencies among different populations.

Polymorphism	Ethnicity	Number of subject	% allele frequency		p-value*
UGT2B7 -161C>T			C	T	
	Thai (this study)	81	75	25	
	Japanese[14]	136	74.6	25.4	0.875
	Japanese[15]	160	75.6	24.4	0.939
	Korean[17]		50	60	40
0.009					
	Spain[20]	53	54.72	45.28	<0.001
	White[18]	64	49	51	<0.001
	Black[18]	25	68	34	0.306
	Norwegian[19]	239	44	56	<0.001

*Chi-square test

As for *UGT2B7*, the results from our study found that *UGT2B7* 372A>G allele frequency in Thai population was not different from those of previously published populations including the Spanish, Japanese and Korean.[14-17, 19] However, *UGT2B7* -161C>T allele frequency in the Thai population was different from that of the Caucasian populations including the Spanish, white Caucasian and Norwegian populations *(P <0.001)*, but the frequency was similar to that of the black Caucasian *(P = 0.306)*.[18-20] Comparing with other Asian populations, the allele frequency of *UGT2B7* -161C>T in our study was comparable to the results obtained from previous studies in the Japanese population, but it was significantly different from that of the Korean population.[14-15, 17]

Discussion

Genetic polymorphisms of drug metabolizing enzymes are known to be one of an important factors contributing to interindividual variations in the metabolisms of drugs. The knowledge of genetic polymorphisms could lead to a more rational and safer drug administration.[1-2] The UGT enzymes play a major role in the metabolism of several xenobiotics and endobiotics. A number of UGT polymorphisms have been identified.[4-5] The polymorphisms of *UGT1A1* are known to be involved in the cause of Gilbert syndrome.[5-6] *UGT1A4* is responsible for the metabolism of several drugs including olanzapine, clozapine, and lamotrigine[9-10, 13], whereas *UGT1A8* and *UGT1A9* are important in the metabolism of mycophenolic acid.[5]

In this study, we investigated the prevalence of four SNPs: *UGT1A4* 142T>G, *UGT1A4* 70C>T, *UGT2B7* 372A>G, and *UGT2B7* -161C>T in 81 Thai patients. The results from this study showed that nearly half of the Thai patients (54%) were wild-type of *UGT1A4* 142T>G. The allele frequency of *UGT1A4* 142T>G in the Thai population was 27%. This number is similar to the value previously reported in the Turkish population (23.26%).[9] Interestingly, comparing

among Asian populations, the allele frequency of *UGT1A4* 142T>G in the Thai population is considered to be higher than the frequency found in the Japanese and Korean populations.[11-13] Although, the polymorphism of *UGT1A4* 70C>T was commonly found in the Caucasian, it was not detected in this Thai population.[8] This finding is similar to the results obtained from the Japanese populations.[12-13] The glucuronidation activity of *UGT1A4* has been investigated. The impact of *UGT1A4* 142T>G polymorphisms on glucuronidation activity depended upon a substrate. An enzyme activity was reduced for b-naphthylamine, benzidine, trans-androsterone and dihydrotestosterone, while it was increased for the glucuronidation of clozapine, olanzapine, and lamotrigine.[8-10] Therefore, the polymorphisms of *UGT1A4* 142T>G should be taken into account for dose adjustment of these drugs in patients.

The allele frequencies of *UGT2B7* 372A>G and *UGT2B7* -161C>T in our study was found to be 20% and 25%, respectively. The allele frequency of *UGT2B7* 372A>G was similar to those previously published in the Asian and Caucasian populations.[14, 16-17, 20] The previous studies showed different allele frequency of *UGT2B7* -161C>T among populations. The studies in Japanese population found the frequency of this variation to be about 25% which is consistent with the finding in our study.[14-15] Interestingly, the study in the Korean population found the allele frequency of this polymorphism to be 40% which is higher than the value reported in our study. However, the study in the Korean population consisted of a small number of patients (50 patients).[17] Therefore, they may not represent the true frequency of this population. owever, it should be noted that the frequency of *UGT2B7* -161C>T in the Asian (Thai and Japanese) populations is lower than that previously reported from the Caucasians.[19-20]

The functional polymorphisms of *UGT2B7* were reported. Whereas, the variation of morphine glucuronidation was not likely to be explained by the variations of *UGT2B7*, the *UGT2B7* -161C>T polymorphism was reported to be associated with lamotrigine concentration- to-dose ratio.[19-20] Therefore, similar to *UGT1A4* 142T>G, it is postulated that the impact of *UGT2B7* variations on glucuronidation activity could be depended on a substrate.

Conclusion

In summary, this is the first study that investigates the genetic variants of *UGT1A4* and *UGT2B7* in the Thai population. The results revealed the variations of *UGT1A4* and *UGT2B7* polymorphisms between the Thais and other ethnicities. These variations could contribute to the difference of the pharmacokinetics of the drugs which are substrates of these enzymes among ethnicities. The reported prevalence of *UGT1A4* and *UGT2B7* polymorphisms in this population provide prior information that can be used for a better design of the study aiming to investigate the association of genetic factors and pharmacokinetics of its substrate.

Acknowledgements

We would like to thank all staffs at epileptic and psychiatric outpatient clinic, Prasat Neurological Institute for their contributions and collaborations. This study was financially supported by Thailand Research Fund (MRG-5480122), the 90th Anniversary of

Chulalongkorn University Fund (Ratchadaphisek-somphot Endowment Fund), and the Faculty of Pharmacy Research Fund.

References

1. Johnson JA. Pharmacogenetics: potential for individualized drug therapy through genetics. Trends Genet 2003 Nov;19(11):660-6
2. Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. Annu Rev Med 2006;57:119-37
3. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics 1998 Aug; 8(4): 283-9
4. Liston HL, Markowitz JS, DeVane CL. Drug glucuronidation in clinical psychopharmacology. J Clin Psychopharmacol 2001 Oct; 21(5): 500-15
5. Maruo Y, Takahashi H, Matsui K, Sato H, Takeuchi Y. Phase II drug metabolism and individualized drug therapy: a focus on functional genetic variation in UDP-glucuronosyltransferases. Curr Pharmacogenomics Person Med 2010 Jun; 8(2): 146-66
6. Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. Pharmacogenomics J 2003; 3(3): 136-58
7. Rowland A, Elliot DJ, Williams JA, Mackenzie PI, Dickinson RG, Miners JO. In vitro characterization of lamotrigine N2-glucuronidation and the lamotrigine-valproic acid interaction. Drug Metab Dispos 2006 Jun; 34(6): 1055-62
8. Ehmer U, Vogel A, Schutte JK, Krone B, Manns MP, Strassburg CP. Variation of hepatic glucuronidation: Novel functional polymorphisms of the UDP-glucuronosyltransferase UGT1A4. Hepatology 2004 Apr; 39(4):970-7
9. Gulcebi MI, Ozkaynakci A, Goren MZ, Aker RG, Ozkara C, Onat FY. The relationship between UGT1A4 polymorphism and serum concentration of lamotrigine in patients with epilepsy. Epilepsy Res 2011 Jun; 95(1-2): 1-8
10. Ghotbi R, Mannheimer B, Aklillu E, Suda A, Bertilsson L, Eliasson E, Osby U. Carriers of the UGT1A4 142T>G gene variant are predisposed to reduced olanzapine exposure-an impact similar to male gender or smoking in schizophrenic patients. Eur J ClinPharmacol 2010 May;66(5):465-74
11. Yea SS, Lee SS, Kim WY, Liu KH, Kim H, Shon JH, Cha IJ, Shin JG. Genetic variations and haplotypes of UDP-glucuronosyltransferase 1A locus in a Korean population. Ther Drug Monit 2008 Feb; 30(1): 23-34
12. Saeki M, Saito Y, Jinno H, Sai K, Hachisuka A, Kaniwa N, Ozawa S, Kawamoto M, Kamatani N, Shirao K,et al. Genetic variations and haplotypes of UGT1A4 in a Japanese population. Drug Metab Pharmacokinet 2005 Apr;20(2):144-51
13. Mori A, Maruo Y, Iwai M, Sato H, Takeuchi Y. UDP-glucuronosyltransferase 1A4 polymorphisms in a Japanese population and kinetics of clozapine glucuronidation. Drug MetabDispos 2005 May; 33(5): 672-5

14. Saeki M, Saito Y, Jinno H, Tanaka-Kagawa T, Ohno A, Ozawa S, Ueno K, Kamakura S, Kamatani N, Komamura K, et al. Single nucleotide polymorphisms and haplotype frequencies of UGT2B4 and UGT2B7 in a Japanese population. Drug Metab Dispos 2004 Sep; 32(9): 1048-54

15. Saito K, Moriya H, Sawaguchi T, Hayakawa T, Nakahara S, Goto A, Arimura Y, Imai K, Kurosawa N, Owada E, et al. Haplotype analysis of UDP-glucuronocyltransferase 2B7 gene (UGT2B7) polymorphisms in healthy Japanese subjects. ClinBiochem 2006 Mar; 39(3): 303-8

16. Hirota T, Ieiri I, Takane H, Sano H, Kawamoto K, Aono H, Yamasaki A, Takeuchi H, Masada M, Shimizu E,et al.Sequence variability and candidate gene analysis in two cancer patients with complex clinical outcomes during morphine therapy. Drug Metab Dispos 2003 May; 31(5): 677-80

17. Hwang MS, Lee SJ, Jeong HE, Lee S, Yoo MA, Shin JG. Genetic variations in UDP-glucuronosyltransferase 2B7 gene (UGT2B7) in a Korean population. Drug Metab Pharmacokinet 2010; 25(4): 398-402

18. Sawyer MB, Innocenti F, Das S, Cheng C, Ramirez J, Pantle-Fisher FH, Wright C, Badner J, Pei D, Boyett JM, et al. A pharmacogenetic study of uridinediphosphate-glucuronosyltransferase 2B7 in patients receiving morphine. Clin Pharmacol Ther 2003 Jun; 73(6): 566-74

19. Holthe M, Rakvag TN, Klepstad P, Idle JR, Kaasa S, Krokan HE, Skorpen F. Sequence variations in the UDP-glucuronosyltransferase 2B7 (UGT2B7) gene: identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients. Pharmacogenomics J 2003; 3(1): 17-26

20. Blanca SM, Herranz JL, Leno C, Arteaga R, Oterino A, Valdizan EM, Nicolas JM, Adin J, Shushtarian M, Armijo JA. UGT2B7_-161C>T polymorphism is associated with lamotrigine concentration-to-dose ratio in a multivariate study. Ther Drug Monit 2010 Apr; 32(2): 177-84

21. Linder MW, Evans WE, HL. M. Application of pharmacogenetic principles to clinical pharmacology. In: Burton ME, Schentag JJ, Shaw LM, Evans WE, editors. Applied pharmacokinetics & pharmacodynamics: Principles of therapeutic drug monitoring. 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2006:168-9