Review Article

นัยสำคัญทางคลินิกของภาวะพหุสัณฐานไซโตโครมพี 450 3 เอ (*CYP3A*)

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บทคัดย่อ

นัยสำคัญทางคลินิกของภาวะพหุสัณฐานไซโตโครมพี 450 3 เอ (*CYP3A*)

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ไซโตโครม พี 450 (CYP450) มีบทบาทสำคัญในการเร่งกระบวนการเมแทบอลิซึมของสารจำพวกไขมันทั้งภายในร่างกายและจากภายนอกร่างกาย นำไปสู่การกำจัดพิษของสารจากภายนอกร่างกายและกระบวนการสลายของสารภายในร่างกาย ภาวะพหุสัณฐาน (polymorphism) ของ *CYP450* เป็นปรากฏการณ์หนึ่งที่บ่งชี้ความหลากหลายของ *CYP450* ซึ่งเป็นสาเหตุของการเปลี่ยนแปลงอัตราการเมแทบอลิซึมและสมรรถนะทางเภสัชวิทยา ภาวะพหุสัณฐานของ *CYP3A* มีรายงานทางคลินิกถึงความเกี่ยวข้องกับความล้มเหลวของการรักษาด้วยยาจากการเปลี่ยนแปลงทางเภสัชจลนศาสตร์ของยา โดยทั่วไป อัลลีลของยีน *CYP3A4*1B*, *CYP3A4*1G* และ *CYP3A5*3* มีความเกี่ยวข้องกับการลดลงของเอนไซม์ CYP3A ตัวอย่างเช่น ผู้ที่มียีน *CYP3A5*3* มีแนวโน้มการเกิดภาวะเจ็บปวดเนื่องจากกล้ามเนื้อถูกทำลายจากอะทอร์วาสแตติน (atorvastatin) ขนาดสูงจากอัตราการกำจัดยาที่ลดลง เมื่อพิจารณาภาวะพหุสัณฐานของ *CYP3A* ต่ออันตรกิริยาของยา ผู้ป่วยที่มียีน *CYP3A5*3* แล้วได้รับโคพิโดเกรล (clopidogrel) ร่วมกับตัวยับยั้งเอนไซม์ CYP3A4 เช่น ไอทราโคนาโซล (itraconazole) จะมีความเสี่ยงของการเกิดโรคท่อเลือดแดงและหลอดเลือดแดงแข็ง (atherothrombotic) เพิ่มสูงขึ้นภายหลังศัลยกรรมตกแต่งหลอดเลือดหัวใจ (coronary angioplasty) เนื่องจากสมรรถนะการสะสมเกล็ดเลือดที่เพิ่มมากขึ้น สำหรับภาวะพหุสัณฐานของ *CYP3A* ต่อภาวะแทรกซ้อนของโรคนั้นพบว่าผู้ที่สูบบุหรี่อย่างหนักไม่ว่าเพศชายหรือหญิงที่มีอัลลีลของยีน *CYP3A4*1B* มีความเสี่ยงของการเกิดมะเร็งปอดเพิ่มมากกว่าผู้ที่มียีน *CYP3A4*1A* ที่สูบบุหรี่น้อยกว่าอย่างมีนัยสำคัญ นิพนธ์ปริทรรศน์ฉบับนี้เป็นการนำเสนอภาพรวมของภาวะพหุสัณฐานของ *CYP3A* และนัยสำคัญทางคลินิกในแง่เภสัชบำบัด 3 ด้าน ได้แก่ เภสัชจลนศาสตร์ อันตรกิริยาของยา และภาวะแทรกซ้อนของโรค

คำสำคัญ : *CYP3A*, ภาวะพหุสัณฐานของ *CYP3A*, เภสัชจลนศาสตร์, อันตกิริยาของยา, ภาวะแทรกซ้อนของโรค

Clinical Significance of Cytochrome *P450 3A* (*CYP3A*) Polymorphism

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Abstract

Clinical Significance of Cytochrome *P450 3A* (*CYP3A*) Polymorphism

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Cytochrome P450 (CYP) plays a major role in catalyzing metabolism of lipophilic endogenous and exogenous substrates, leading to detoxification of exogenous compounds and catabolism of endogenous compounds. Polymorphism of *CYP450* is a phenomenon of variation of *CYP450* that causes alteration in metabolic rate and pharmacological activity. *CYP3A* polymorphism has been clinically reported to be associated with failure of medication from a change of pharmacokinetics. *CYP3A4*1B*, *CYP3A4*1G*, and *CYP3A5*3* alleles are mostly involved in reduction of CYP3A enzymes. For example, *CYP3A5*3* carriers exhibited a tendency to be suffered from high dose of atorvastatin-induced muscle damage due to lower clearance of the drug. Considering *CYP3A* polymorphism on drug interactions, *CYP3A5*3* patients who received clopidogrel concomitantly with CYP3A4 inhibitors, e.g. itraconazole, have increased the risk of atherothrombotic event after coronary angioplasty according to higher platelet aggregation activity. Concerning *CYP3A* polymorphism on disease complications, heavy smokers of both sexes with *CYP3A4*1B* allele were significantly found an increase in a risk of lung cancer than those of *CYP3A4*1A* with lower smoking. The present review article brings an overview of *CYP3A* polymorphism and its clinical significance on 3 pharmacotherapeutic aspects, including pharmacokinetics, drug interactions, and disease complications.

Keywords : *CYP3A*, *CYP3A* polymorphism, pharmacokinetics, drug interactions, disease complications

1. Introduction to Cytochrome P450 3A (*CYP3A*)

Cytochrome P450 (CYP), a superfamily of heme-containing protein, plays a major role in metabolism of lipophilic endogenous substances, e.g. steroid derivatives and bile acid, and exogenous substrates, e.g. drugs, natural chemicals in food (de Wildt *et al.*, 1999). Metabolism of foreign chemicals by CYP leads to detoxification; however, the actions of CYP can also cause toxic metabolites, and subsequently a risk of adverse or toxic effects. The most abundant isoform of *CYP* in human body is *CYP3A* (50%), followed by *CYP2D6* (30%), and *CYP2E1* (2%) (Zhou *et al.*, 2009). Hence, to collect and analyze data of *CYP3A* is essential. Nuclear receptors involving in regulation of *CYP3A* are pregnane X receptor (PXR), constitutive androstane receptor (CAR), and glucocorticoid receptor (GR) (Squires *et al.*, 2004). Metabolism related gene regulation of *CYP3A* by PXR and CAR was specific in human other than rodents. Therefore, extrapolation of *in vivo* results from murine to human may not be completely corresponded (Kliewer *et al.*, 2002; Squires *et al.*, 2004).

Genetic variation of drug metabolizing enzymes resulting in inter-individual variation of pharmacokinetics called 'polymorphism' is the most important uncontrollable factor and is one of the main causes of variation in drug metabolism (Ingelman-Sunberg, 1999). Polymorphism of *CYP* is a state of variation of CYP activity leads to unpredictable outcome of treatments such as failure of medication or drug toxicity, drug interaction that contribute to CYP inhibitors/inducers, and complication with diseases related to metabolism.

2. Significance of *CYP3A*

CYP3A is located on chromosome 7 (Nagata and Yamazoe, 2002). It plays a major role in drug metabolism in human liver and intestine (McKinnon *et al.*, 1995). *CYP3A* consists of 4 functional genes, namely *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*. *CYP3A4* is the most abundant in human liver and plays an essential role in oxidative metabolism of clinical drugs whilst *CYP3A5* is present 20-25% in adult liver. *CYP3A7* is the majority in fetal liver (Kivisto *et al.*, 1996). *CYP3A43* is the most recent found (Domanski *et al.*, 2001; Lamba *et al.*, 2002) which plays a role in hormone metabolism (Domanski *et al.*, 2001; Koch *et al.*, 2002).

CYP3A4 is accounted for 30-40% of *CYP* in human liver and intestine. It is located in chromosome 7 at band q22.1 and divided into 13 exons and 12 introns with approximately length of 27 kbp (Hashimoto *et al.*, 1995). CYP3A4 metabolizes lipophilic drugs in positions dictated by hydrogen abstraction in form of *C*-hydroxylation, or electron abstraction in form of *N*-dealkylation as shown in Table 1.

Table 1. Cytochrome P450 3A4 substrates, inhibitors, and inducers (Adapted from Michalets, 1998)

Substrates					
Alprazolam	Amlodipine	Atorvastatin	Cannabinoids	Carbamazepine	Clindamycin
Cyclophosphamide	Cyclosporine	Dapsone	Dexamethasone	Diazepam*	Erythromycin
Estrogen	Doxorubicin	Etoposide	Fentanyl	Fexofenadine	Ifosfamide
Imipramine	Indinavir	Lansoprazole*	Lidocaine	Losartan	Lovastatin
Miconazole	Midazolam	Nicardipine	Nifedipine	Odansetron	Paclitaxel
Pravastatin	Prednisolone	Quinidine	Quinine	Rifampin	Ritonavir
Sertraline	Tacrolimus	Tamoxifen	Temazepam	Terfenadine	Testosterone
Verapamil	Vinblastine	Vincristine	R-warfarin		
Inhibitors					
Amiodarone	Cannabinoids	Clarithromycin	Fluconazole	Fluoxetine	Fluvoxamine
Grapefruit juice	Indinavir	Itraconazole	Ketoconazole	Omeprazole*	Metronidazole
Miconazole	Norfloxacin	Quinine	Ritonavir		
Inducers					
Carbamazepine	Dexamethasone	Ethosuximide	Phenobarbital	Phenytoin	Rifampin

Note. * minor

CYP3A5 is also found in human liver. It is homologous to *CYP3A4* (83%) but present at lower level than *CYP3A4* (McKinnon *et al*, 1995) with large inter-individual variation (Kuehl *et al.*, 2001). Even the substrate specificity of CYP3A5 was quite similar to those of CYP3A4; the difference in catalytic properties has been found (de Wildt *et al*., 1999).

CYP3A7 is a constitutive isoform in embryonic, fetal, and newborn liver but it is detectable in adult liver at very lower (Tateishi *et al.*, 1997). Its important role is biotransformation of endogenous substances. CYP3A7 catalyzes 16 α- hydroxylation of dehydroepiandrostone sulfate (DHEA- S), a reaction involving in formation of estradiol in pregnancy, with greater affinity and maximum velocity than CYP3A4 (Ohmori *et al.*, 1998). Moreover, CYP3A7 can metabolize carcinogen such as aflatoxin B1 (Hashimoto *et al*., 1995).

CYP3A43 is the most recent found of the *CYP3A* subfamily (Domanski *et al.*, 2001; Lamba *et al.*, 2002) expressed dominantly in prostate and few in kidney, pancreas, and testis. It is expressed only 0.3% of *CYP3A* in liver and plays a role in hormone metabolism (Domanski *et al.*, 2001; Koch *et al.*, 2002). However, a major role in xenobiotic metabolism of CYP3A43 has not been indicated yet (Domanski *et al*., 2001).

3. Polymorphism of *CYP3A*

Polymorphism of *CYP* is related in occurrence of adverse drug reactions (Ingelman-Sunberg, 1999). *CYP3A4* consists of more than 19 variants and a series of sub-variants, **1B* through **20*, have been identified. *CYP3A4*1A* is defined as the wild type. There are 1641 single nucleotide polymorphism (SNP)[#] in *CYP3A4* sequences in NCBI dbSNP (http://www.ncbi.nlm.nih.gov/, accessed on June 14, 2018). The first *CYP3A4* polymorphism is *CYP3A4*1B* (-392A>G) which occurs in Caucasians about 2- 9% and higher in Africans. To Asian ethnic groups, *CYP3A4*1B* is absent in Japanese (Klein and Zanger, 2013; Zhou *et al.*, 2009). The *CYP3A4*2* consisting a 664T>C SNP was found 2. 7% in Caucasians but it was not found in Africans and Chinese. *CYP3A4* 2* allele encodes a CYP enzyme compared to the wild-type with substrate-dependent altered kinetics (Sata *et al.*, 2000). The allele frequency of *CYP3A4*3* with a 1334T>C SNP was found in Caucasians about 1. 1% (van Schaik *et al.*, 2001; Garsa *et al.*, 2005). *CYP3A4*4* and *CYP3A4*5* consist of 352A>G and 653C>G, respectively (Lamba *et al*., 2002). *CYP3A4*6* allele leads to early stop codon by a frame shift mutation (831insA) arising from an A17776 insertion in exon 9 (Hsieh *et al.*, 2001). Hence, *CYP3A4*6* allele participates in decresing CYP3A4 activity in Chinese. When compared with healthy Chinese population data, *CYP3A4* 3,* 4,* 5* and ** 6* allele may participate in decreasing CYP3A4 activity (Hsieh *et al.*, 2001).

CYP3A5 consists of at least 10 variants *(*1B to *11)*. The wild type allele and normal enzyme expression is *CYP3A5*1* (Kuehl *et al.*, 2001). The most allele relevant to *CYP3A5* is *CYP3A5*3* (6986A>G) as it is approximately found in Caucasian (85%) and African American (48%). Mutation at intron 5 junction leading to abnormal splicing and defective enzyme is *CYP3A5*5* (Chou *et al.*, 2001). *CYP3A5* 6*, mutation in exon 7, is relatively frequent in African Americans and results in deletion of exon from mRNA (Kuehl *et al.*, 2001). *CYP3A5* 7* participates in insertion of single nucleotide in the sequence resulting in termination of translation (Hustert *et al.*, 2001). CYP3A5 is primarily extrahepatic CYP enzyme, hence polymorphic expression is observed in metabolism of endogenous steroids or xenobiotics in extrahepatic organs. As in renal, *CYP3A5* 1/* 3* genotype contains at least 8- fold *CYP3A5* expression and 18- fold catalytic activity higher than *CYP3A5*3/*3* genotype (Givens *et al*., 2003). For example, pediatric heart transplant patients carried *CYP3A5* 1/* 3* genotype required higher dose of tacrolimus than those with *CYP3A5*3/*3* genotype (Zheng *et al*., 2003).

[#1]Single Nucleotide Polymorphism (SNP) is a DNA sequence variation when a single nucleotide in the genome differs between members of a species or paired chromosomes in an individual. These changes may cause disease, or correlate with drug response and other phenotypes.

CYP3A7 polymorphism is mostly found in *CYP3A7*1* variant. *CYP3A7*1C* variant (291G>T) is the most common and found in Caucasians (3%) and African-Americans (6%) (Kuehl *et al*., 2001). *CYP3A7*1C* significantly increased *CYP3A7* expression (Burk *et al*., 2002).

4. Clinical Impacts of *CYP3A* Polymorphism

4.1 *CYP3A* Polymorphism on Pharmacokinetics

Genetic polymorphism of CYP3A5 on cyclosporine and tacrolimus concentration - Cyclosporine A (CsA) and tacrolimus are calcineurin inhibitors which are primary immunosuppressant used in organ transplantation. CsA and tacrolimus improve allograft survival by reducing graft rejection (Ponticelli *et al*., 2002). CsA and tacrolimus have narrow therapeutic index in variable pharmacokinetics and they are mostly metabolized by CYP3A4 and CYP3A5 while CYP3A5 inter-individually expresses more dominant to CYP3A4 (Crettol *et al*., 2008; de Jonge *et al*., 2012). To investigate whether *CYP3A5*3* affects pharmacokinetics of CsA and tacrolimus, two groups of patients including *CYP3A5*1/*3* genotype (expresser) and *CYP3A5*3/*3* (non-expresser), were divided. Pharmacokinetics (C_0, C_0/dose and dose) were examined at 3, 6, and 12 months (Zhao *et al*., 2005). The pharmacokinetics of CsA from two groups, C_0, dose-adjusted C_0 and dose, were not significantly different at all-time points. For tacrolimus, only C_0 was not significantly different between both groups. But the dose and dose-adjusted C_0 of tacrolimus were significantly higher and lower, respectively, in the expresser group compared to non-expresser. These findings suggested that *CYP3A5*3/*3* resulted in the loss of metabolic CYP3A5 activity. Moreover, the expressers needed more tacrolimus to achieve target blood concentration than those of non-expressers. Hence, the *CYP3A5*1/*3* carriers might have a higher risk of under-immunosuppression and graft rejection than the *CYP3A5*3/*3* (Zhao *et al*., 2005).

CYP3A genotype and concomitant medication on severity of atorvastatin-induced muscle damage - Atorvastatin is HMG-CoA reductase inhibitor which is prescribed as cholesterol lowering agent (Jones *et al*., 2003). Atorvastatin-induced muscle damage may be contributed to an increase in muscle enzymes monitored *via* creatine kinase (CK) blood level (Black *et al*., 1998). Moreover, onset of statin-induced muscle damage is faster when concomitant with other lipid-lowering agents (Duell *et al*., 1998). Atorvastatin is metabolized by CYP3A4 and CYP3A5 enzymes (Park *et al*., 2008). *CYP3A4*1B* and *CYP3A5*3* are the most common *CYP3A* polymorphism (Kuehl *et al*., 2001). To investigate whether CYP3A polymorphism and concomitant medication affect risk and severity of atorvastatin-induced muscle damage, a retrospective case control study was performed. The association between *CYP3A* genotypes (*CYP3A4*1B* and *CYP3A5*3*) and both risk and severity of myopathy or muscle damage was estimated through serum CK level (Wilke *et al*., 2005). Both *CYP3A4*1B* and *CYP3A5*3* carriers were not significantly increased risk of muscle damage compared to the wild-type control (*CYP3A4*1*, P=0.519 and *CYP3A5*1*, P=0.468 respectively). However, *CYP3A5*3* carriers especially *CYP3A5*3/*3* genotype showed a tendency to increase severity of muscle damage in term of serum CK elevation without concomitant medication (P=0.025 without gemfibrozil and P=0.010 without gemfibrozil and niacin) (Wilke *et al*., 2005). These results indicated that the patients who have developed atorvastatin-induced myalgia were suffered from the higher degree of muscle damage, though *CYP3A* polymorphism did not affect the risk of muscle damage (Wilke *et al*., 2005).

CYP3A4* 1G polymorphism on CYP3A activity and response to fentanyl - Fentanyl, a synthetic opioid prescribed for anesthesia or analgesia inter- individually varies in an effective dose for pain control (Gourlay *et al*., 1988). Requirement of fentanyl dosage during abdominal operation differed up to 5-fold among patients (Labroo *et al*., 1997). Fentanyl is mainly metabolized in the liver *via* CYP3A4. *CYP3A4*1G* allele is highly presented in Asian, 24.9% in Japanese and 22.1% in Chinese (Du *et al*., 2007). The patients with homozygous *CYP3A4* 1G/ * 1G* had

significantly lower CYP3A4 activity than those of wild-type genotype (*CYP3A4* 1/ * 1*, P<0.05) and heterozygous *CYP3A4* 1/ * 1G* (P<0.05). Moreover, the patients with homozygous *CYP3A4* 1G/ * 1G* genotype required less fentanyl to control pain than those carrying wild-type (P<0.05) and heterozygous (P<0.05) genotypes. However, there was no significant difference in the risk of adverse effect among genotype variation (P>0.05) (Zhang *et al.*, 2009). Therefore, the *CYP3A4*1G/*1G* carriers have lower CYP3A4 activity, leading to lower fentanyl requirement for the post-operation. However, the others, such as CYP3A5, participate in fentanyl metabolism, hence further observation in homozygous *CYP3A5*3* may help prediction on response of fentanyl-pain control (Zhang *et al.*, 2009).

4.2 *CYP3A* Polymorphism on Drug Interaction

Polymorphism of CYP3A5 and clopidogrel on risk of atherothrombotic events - Clopidogrel is an antiplatelet drug used in treatment of coronary artery disease. It is a prodrug which needed to be metabolized by CYP3A isoenzymes to be in an active form. Metabolism of clopidogrel was mostly involved with CYP3A4 and CYP3A5 (Clarke and Waskell, 2003). If a drug is metabolized equally by CYP3A4 and CYP3A5, the overall rate of metabolism is sum of CYP3A4 and CYP3A5 metabolic rates. *CYP3A5* is expressed polymorphically in the liver, particularly in Caucasian (30%) and African-American (50%) (Kuehl *et al.*, 2001), and may contribute to hepatic CYP3A activity, at least 50%, in three quarters of white people and in half of black people (Evans and McLeod, 2003). Thus, a change in CYP3A5 may lead to differentiation of pharmacokinetics of the drug. *CYP3A5* gene is divided by functional polymorphism as 'expresser' (*CYP3A5* 1*) and 'non-expresser' (*CYP3A5*3*) alleles (Kuehl *et al.*, 2001). Impacts of *CYP3A5* genotype on clopidogrel treatments were examined by Suh *et al.* (2006); phase 1 was association of *CYP3A5* genotype and antiplatelet activity as platelet aggregation after taking clopidogrel with and without a CYP3A inhibitor and phase 2 investigated an association of *CYP3A5* genotype on risk of atherothrombotic events in patients taking clopidogrel after coronary angioplasty by percutaneous transluminal coronary intervention (PCI). After treatment with itraconazole (a CYP3A4 inhibitor), clopidogrel was significantly inhibited platelet aggregation in the *CYP3A5* expresser genotype. On the other hand, among the *CYP3A5* non-expressers, clopidogrel showed a significant platelet aggregation only on day 7. These observations revealed a significant change in the *CYP3A5* expresser genotype greater than those *CYP3A5* non-expresser genotype (Suh *et al.*, 2006). During 6 month-follow up in phase 2, atherothrombotic events were observed in 17 patients with stent implantation; these events occurred more frequently among the 14 non-expressers than those of 3 expressers (Suh *et al.*, 2006). These observations indicated that clinical outcomes after coronary angioplasty with stent implantation were differed by concomitant administration of clopidogrel with itraconazole among *CYP3A5* non-expressers. Moreover, the non-expressers were vulnerable in an increase in atherothrombotic risk after the stent implantation.

Polymorphism of CYP3A5 on drug interaction of tacrolimus and fluconazole in renal allograft - Tacrolimus is an immunosuppressant for prevention of renal allograft rejection. In addition, tacrolimus is marked as a narrow therapeutic drug due to nephrotoxicity, neurotoxicity, and infectious complications (Kuypers *et al.*, 2004). Tacrolimus is metabolized by CYP3A4 and CYP3A5. Azole antifungals, e.g. fluconazole, have inhibitory activity on CYP3A enzymes; hence, drug interaction leads to tacrolimus toxicity or sub-therapeutic tacrolimus exposure if inaccurate adjustment after discontinuing of azole antifungals (Paterson and Singh, 1997). In addition, polymorphism of *CYP3A5* are varied inter-individually and related to clinical variability and dose adjustment of tacrolimus (Goto *et al.*, 2004; Kuypers *et al.*, 2004; Kuypers *et al.*, 2008). Pharmacokinetics of tacrolimus were obtained from patients with *CYP3A5* 1/ * 1, CYP3A5*1/*3* and *CYP3A5*3/*3* concomitantly received fluconazole as antifungal treatment. Homozygous *CYP3A5*3* carriers had significantly higher dose-corrected

through blood tacrolimus concentration during fluconazole treatment than heterozygous *CYP3A5*1* carriers (3.28±2.34-fold, P=0.04). Moreover, there were significant reductions of weight- corrected dose tacrolimus requirements during fluconazole treatment from the baseline in homozygous *CYP3A5*3* carriers (54.7±23.7%, P<0.05) (Kuypers *et al.*, 2008). In summary, *CYP3A5*3* (non-expressers) allele was more sensitive to fluconazole- induced tacrolimus inhibitory metabolism than those *CYP3A5* 1* carriers. *CYP3A5* 3* carriers might increase the risk of tacrolimus toxicity during fluconazole treatment. Limitation of the study were 1) other azole antifungals such as ketoconazole, itraconazole, and voriconazole were not simultaneously investigated to confirm analogous effect of fluconazole, and 2) genotyping analysis was operated after occurrence of drug interaction, thus the numbers of *CYP3A4*1B* were too low (only two patients) for formal analysis and interpretation (Kuypers *et al*., 2008).

***CYP3A5*3* polymorphism on pharmacokinetic associated drug interaction between tacrolimus and amlodipine -** Renal transplantation is the most practical renal replacement therapy. Hypertension has been extensively indicated as a risk factor for graft rejection, consequently shorter life expectancy. Therefore, a decrease in the risk of post-transplant hypertension possibly lowered graft rejection and increased life expectancy (Opelz and Dohler, 2005). Amlodipine is a calcium channel blocker used for management of hypertension during renal transplantation. Due to its long half-life (35-50 hours), amlodipine maintains stable blood pressure and leads to improvement of renal function (Leenen *et al*., 2007; Mangray *et al*., 2011). Immunosuppressive therapy in renal transplantation in order to prevent graft rejection consists of a calcineurin inhibitor tacrolimus (Ponticelli *et al*., 2002). Both amlodipine and tacrolimus are mainly metabolized by CYP3A in the liver (Michalets, 1998; Iwasaki, 2007). Moreover, tacrolimus clearance is higher in CYP3A5 than CYP3A4 (Bader *et al*., 2000). *CYP3A5*1*, the wild-type allele, expressed high level of CYP3A5 enzymes in contrast to *CYP3A5*3* allele (Kuehl *et al*., 2001). A randomized crossover study was performed in 102 healthy Chinese volunteers to investigate the effect of *CYP3A5*3* allele on pharmacokinetics associated drug interaction between tacrolimus and amlodipine. The pharmacokinetics study of tacrolimus and amlodipine followed by a single- and multiple-dose were performed for 14 days (Zuo *et al*., 2013). In both single- and multiple-dose studies, *CYP3A5*1* carriers showed higher oral clearance (CL/F) of tacrolimus than those of *CYP3A5*3* carriers (3.8-fold, P=0.008). In contrast, the CL/F of amlodipine was higher in *CYP3A5*3* carriers than those of *CYP3A5*1* carriers (2.0-fold, P=0.001). Moreover, mean tacrolimus CL/F was significantly decreased by amlodipine in the *CYP3A5*3* carriers (2.2-fold, P=0.005), in contrast to the *CYP3A5*1* carriers. Amlodipine CL/F was significantly increased by tacrolimus in *CYP3A5*1* (1.4-fold, P=0.016) (Zuo *et al*., 2013). Estimation of tacrolimus and amlodipine CL/F was associated with *CYP3A5*3* allele. *CYP3A5*1* carriers required higher dosage of tacrolimus to achieve desired blood concentration than those *CYP3A5*3* carriers. However, if tacrolimus is concomitantly prescribed with amlodipine, the dosage of tacrolimus should be lower in *CYP3A5*1* carriers to achieve desired blood concentration. Therefore, the dose adjustment of tacrolimus co-administered with amlodipine in *CYP3A5*3* carriers might be considered (Zuo *et al*., 2013).

4.3 *CYP3A* Polymorphism on Disease Complications

CYP3A4 and CYP3A5 genotypes related risk of prostate cancer - Prostate cancer is the most general nonskin-related malignancy and the second cause of death in men (Jemal *et al*., 2002). Risk factors of prostate cancer include age, ethnicity, family history, and diet (Pienta and Esper, 1993). A family history is considered as gene polymorphism, accordingly regulation of metabolism, biosynthesis and regulation of androgen in form of occurrence and progression of prostate cancer (Coughlin and Hall, 2002). CYP3A4 and CYP3A5 enroll androgen, particularly testosterone metabolism (Gibson *et al*., 2002). Association between *CYP3A4*1B, CYP3A5*3* alleles, or

CYP3A4/CYP3A5 haplotypes, and prostate cancer was investigated by family-based case-control study. *CYP3A4*1B* variant was associated with prostate cancer among Caucasians with more aggressive disease (odds ratio (OR) 1.91, 95% confidence interval (CI) 1.02-3.57, P=0.04). In contrast, there was complicate in association between *CYP3A5* variant and prostate cancer risk in disease aggressiveness. Interestingly, *CYP3A4*1B/ CYP3A5*3* haplotype encoding a nonfunctional CYP3A protein was positively associated with prostate cancer risk (OR 2.91, 95% CI 1.36–6.23, P=0.006). Moreover, haplotype *CYP3A* alleles (*CYP3A4*1A* and *CYP3A5*1*) were inversely related with less aggressive prostate cancer. Aggressive prostate cancer was associated with *CYP3A4*1B* allele and *CYP3A4*1B/CYP3A5*3* haplotype (Plummer *et al*., 2003).

Polymorphism of CYP3A on risk of lung cancer - Histological distribution of lung cancer is markedly different in smokers and non-smokers. Lung cancer such as small cell lung cancer (SCLC) and squamous cell carcinoma (SCC) are associated with tobacco smoking (Muscat and Wynder, 1995). CYP3A4 and CYP3A5 metabolize procarcinogens from tobacco smoke in lung to active carcinogens which are polycyclic aromatic hydrocarbons, e.g. benz(*a*)pyrene (Shou *et al*., 1996; Piipari *et al*., 2000) whilst CYP3A4 plays a role in activation of tobacco specific carcinogen *N'*–nitrosornicotine (NNN) in liver (Patten *et al*., 1997). *CYP3A5*1* allele exhibited more activity than *CYP3A5*3* allele (Kuehl *et al*., 2001). Hence, both *CYP3A4* and *CYP3A5* polymorphism might functionally involve in inter-individual risk of lung cancer. Involvement of *CYP3A* polymorphism and tobacco smoking related lung cancer risk was investigated with histological category, gender, and heterozygous or homologous of *CYP3A* genotypes (Dally *et al*., 2003). A case-control study was performed in 801 Caucasian lung cancer patients with adenocarcinoma, SCC and SCLC. *CYP3A4*1B* was significantly elevated SCLC (OR 2.25, 95% CI 1.11–4.55, P=0.02). After co-variation was controlled, an increase in lung cancer risk was found in women rather than men (OR 3.04, 95% CI 0.94–9.90, P=0.06). Both heavy men and women smokers (more than 20 pack-years) with *CYP3A4*1B* allele were significantly found an increase in risk of lung cancer than the lower smoking (less than 20 pack-years) and those carried *CYP3A4*1A/*1A* (OR 3.42, 95% CI 1.65–7.14, P=0.001 and OR 8.00, 95% CI 2.12–30.30, P=0.005, respectively). Interestingly, only homozygous *CYP3A5*1* allele did not increase lung cancer risk (OR 5.24, 95% CI 0.85–102.28, P=0.14). The findings suggested that all histological types of lung cancer-related smoking, except SCLC, were not associated with *CYP3A4*1B*. Moreover, women were found association between *CYP3A4* polymorphism and elevation of lung cancer risk (Dally *et al*., 2003).

Polymorphism CYP3A4 on risk of coronary heart disease - Coronary heart disease (CHD) is one of the most leading causes of death (Gaziano *et al*., 2010). CHD is involved with many risk factors including genetic factor. Sex-hormone associated disease, CHD, has been reported to be relatively increased by CYP (Lee *et al*., 2007). Especially, CYP has been indicated relating onset, prognosis, and progression of CHD (Chaudhary *et al*., 2009). *CYP3A* plays a role in metabolism of endogenous substances including steroid compound, e.g. sex hormones (Lee *et al*., 2001). CYP3A4 is correlated in metabolism of estradiol (Lee *et al*., 2001). Estrogen delays development of CHD by adjusting plasma lipoprotein and suppressing arterial thrombosis (Williams *et al*., 1990; Rossouw, 2002). Therefore, *CYP3A4* polymorphism might influence estradiol metabolism. *CYP3A4*1G* has been found recently in Asian (22.1% in Chinese and 24.9% in Japanese) and it increased CYP3A4 activity (Fukushima-Uesaka et al., 2003; Du et al., 2006; Zhang *et al*., 2010; Uesugi *et al*., 2013). Hence, *CYP3A4*1G* associated risk of CHD was examined by retrospective analysis in 628 Chinese (322 unrelated patients with CHD and 306 age- and sex-matched healthy) and *CYP3A4* genotyping (He *et al*., 2010). Higher risk of CHD was found in *CYP3A4*1G/*1G* patients than *CYP3A4*1* carriers (OR 3.84, 95% CI 1.32-12.65, P=0.025) after conventional risk

factors were adjusted. Moreover, a gender-dependent frequency was found; female who carried *CYP3A4*1G/*1G* genotype had higher CHD risk than the controls (OR 3.02, 95% CI 1.08-8.70, P=0.034) while no risk-difference in *CYP3A4*1G/*1G* was noted in male (He *et al*., 2010). In summary, association between *CYP3A4*1G/*1G* and CHD had been found, especially in female with *CYP3A4*1G/*1G* genotype. These events might be explained by an increase in metabolism of endogenous sex-hormone *via* CYP3A4 leading to a lack of vascular homeostasis. In addition, these findings might be helpful in pathological study and prevention of CHD, particularly in female (He *et al*., 2010).

5. Conclusion

CYP3A enzyme metabolizes both endogenous and exogenous substances and it is the most abundant isoform in human body (50%) mostly in liver and intestine. *CYP3A* subfamily composes of 4 functional genes, namely *CYP3A4, CYP3A5, CYP3A7*, and *CYP3A43*. *CYP3A4* is expressed about 30–40% of *CYP* and contains more than 19 variants, *CYP3A4*1B* to *CYP3A4*20*. *CYP3A5*, a homologous of *CYP3A4*, is mostly found in liver with less abundant than *CYP3A4* and its substrate selectivity is similar to *CYP3A4*. *CYP3A5* contains at least 10 variants, *CYP3A5*1B* to *CYP3A5*11*. *CYP3A5*3* allele is the most present in human (85% Caucasians and 48% African American). *CYP3A5*3, *5, *6,* and *7* alleles are related to termination of translation leading to lower CYP3A5 activity. *CYP3A5* is expressed outside liver, hence its polymorphism influences metabolism in extrahepatic organs. *CYP3A7* is presented in embryonic, fetal, and newborn liver. The relevant role of CYP3A7 is metabolism of endogenous substances such as DHEA-S which is related to estradiol formation. *CYP3A7*1C* allele is a *CYP3A7* polymorphism; however, no clear function has been indicated. *CYP3A43* is the most recent found which is expressed only 0.3% of *CYP3A* in the liver. *CYP3A43* has not been reported a major role in drug metabolism.

Polymorphism of *CYP* is a state of variation of CYP activity, leading to unpredictable outcome of drug treatment, drug interaction, and disease complications. Patients with *CYP3A5*1/*3* increased a risk of graft rejection due to higher CYP3A5 activity for metabolism of an immunosuppressant tacrolimus, resulting in under the target blood concentration. *CYP3A5* 3* carriers lowered atorvastatin clearance, becoming more suffering from atorvastatin-induced muscle damage. *CYP3A4* 1G/ * 1G* carriers deceased CYP3A4 activity, leading to less fentanyl dosage required for abdominal operation. Regarding *CYP3A* polymorphism on drug interaction, *CYP3A5*3* (non-expressers) who received clopidogrel with itraconazole had higher risk of atherothrombotic event after coronary angioplasty from an increase in platelet aggregation activity. In addition, *CYP3A5*3* allele was more sensitive to fluconazole-induced tacrolimus inhibitory metabolism than those *CYP3A5* 1* carrier, leading to a risk of tacrolimus toxicity during co-treatment with fluconazole. To concomitant prescribing of tacrolimus and amlodipine, a decrease in dosage of tacrolimus was required in *CYP3A5*1* carrier. According to *CYP3A* polymorphism on disease complications, *CYP3A4*1B* carriers and *CYP3A4*1B/CYP3A5*3* haplotype exhibited an increased risk of higher grade prostate cancer. Heavy smokers (more than 20 pack-years) of both sexes with *CYP3A4*1B* allele were significantly increased a risk of lung cancer than those lower smokers of *CYP3A4*1A/*1A*. Female who carries *CYP3A4* 1G/ * 1G* genotype showed higher risk of CHD. Hence, *CYP3A4* 1B, CYP3A4* 1G*, and *CYP3A5* 3* alleles are involved in reduction of CYP enzymes, leading to lower metabolism. *CYP3A* polymorphisms have a variety of ethnic diversity. Asian (Chinese and Japanese) carries *CYP3A5*3* are less than Caucasian. In contrast, Caucasian carries *CYP3A4* 1B* whilst *CYP3A4* 1B* is absent in Japanese. Failure of pharmaceutical treatment, drug interaction, and disease complication related to *CYP* polymorphisms had been complicatedly noticed without pharmacogenomics study. Moreover, implementation of *CYP3A* allele information to customize (modify, switch or discontinue) medication for a patient may avoid/ reduce medication error, e. g. drug

interaction and disease complication, due to *CYP3A4* polymorphism. Thus, investigation of *CYP* polymorphism especially a variety of ethnics is significantly impact.

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