CYP3A5*3 Polymorphism and Its Clinical Implications and Pharmacokinetic Role

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Introduction

Interindividual variability in pharmacokinetics including drug absorption, distribution, metabolism, and elimination, which can arise from either genetic or non-genetic origins, is a main factor in the development of therapeutic failure or toxicity. Cytochrome P450 is the heme-containing superfamily of enzymes responsible for the metabolism of a variety of diverse substrates, including xenobiotics. Additionally, these enzymes are involved in the metabolism of cholesterol, steroid hormones and other lipids that are important in intracellular signaling pathways.[1]

The cytochrome P450 (CYP) 3A subfamily is estimated to participate in the biotransformation of 50% of the currently prescribed drugs. Four members of the CYP3A subfamily have been identified in humans: CYP3A4, CYP3A5, CYP3A7, and CYP3A43. Initial data suggested that CYP3A5 accounts for only a small proportion of the total hepatic CYP3A in about 20% of samples, but it was later revealed that CYP3A5 represents more than 50% of the total CYP3A amount in some individuals. Several genetic variants have been described for the CYP3A5 gene, of which the CYP3A5*3 allele (gA6986G), the most common form and leading to the loss of CYP3A5 activity, has been extensively investigated in the aspect of pharmacokinetics and disease risk. This review summarized the molecular characteristics of the CYP3A5 gene, and discusses the association of the CYP3A5*3 polymorphism with disease risks such as cancer and hypertension, along with its role in the pharmacokinetics of CYP3A substrates.

Genetic polymorphism of CYP3A5

Wrighton et al. first reported large interindividual variability of CYP3A5 expression in the liver in 1990,[10] but Jouaidi et al. was the first to report a polymorphism at the 5'-upstream region (CYP3A5*1A) in the aspect of pharmacogenetics.[11] Paulussen et al. then described its genetic basis for the modification of CYP3A5 expression.[12] They showed a clear bimodality in the drug metabolism of the CYP3A5 phenotype, and identified two linked mutations in the promoter region, -45A>G and -368T>G, which were associated with the expres-
sion and activity of the CYP3A5 protein. Notably, the mutation at the site of -45A>G is located in the basic transcription binding element (BTE) of CYP3A5. This mutation may interfere Sp1 binding, thus reducing CYP3A5 gene transcription, to result in lower protein expression in the variant allele with -45A. Lee et al. later identified various SNPs in the 5′-upstream region of the CYP3A5 gene.[13] They found 34 SNPs of CYP3A5, including 27 previously unidentified SNPs, by direct sequencing of the exons, intron-exon junctions and 5′-upstream region of CYP3A5 from 92 racially diverse individuals. The majority of these SNPs occurred in African-American, while only one or two were observed in Asians and Caucasians. However, the small sample size, around 24, might have had limitations to finding other variants, and to accurately reveal the occurrence of SNPs in diverse ethnic groups.

The first genetic variant found in the coding region of the CYP3A5 gene was the CYP3A5*2 allele, which was identified in heterozygotes at a frequency of 3 in 10.[14] This mutation is located in exon 11 at the position of 1289C>A, which produces a change in the amino acid at position 398 (threonine → asparagine). As described above, Kuehl et al. first described the role of the CYP3A5*3 polymorphism mechanistically.[4] This SNP was reported in all ethnic groups, and is thus considered the most ancient allele.[15] The allele frequency of CYP3A5*3 among East Asian populations (Korean, Chinese, and Japanese) is 75–79%, and also occurs in Malay (61%), Indian (59%), African-American (34%), Caucasians (91–94%) and Hispanics 76%.[16–20] In this allele, a guanine at the position of 6986 creates a cryptic splicing site in intron 3, which leads to aberrant splicing of the transcript to cause truncation of the CYP3A5 protein, which results in no enzyme activity.[9,10] This polymorphic allele is strongly associated with the reduced drug clearance of CYP3A substrates, assuming higher drug levels of the CYP3A substrates in the subjects possessing this allele. Because it has a relatively high frequency and occurs in diverse populations, its roles have been extensively investigated. We discussed it further here.

CYP3A5*4 is a coding SNP located in exon 7, which produces an amino acid substitution from glutamine to arginine at the position of the 206th amino acid (Q200R).[21] In the case of CYP3A5*5, it was first described in a Chinese population, representing 12952T>C substitution located in intron 5, which leads to the formation of an alternatively spliced mRNA like CYP3A5*3, and presumably decreased CYP3A5 protein activity.[21] Both CYP3A5*4 and CYP3A5*5 are rare mutations, present only in Chinese at less than 1% frequency.[21] The CYP3A5*6 allele leads to the skipping of exon 7 in transcripts. It is found with an allele frequency of 17% in African-Americans, but is absent in Asian populations.[1,21] A single base insertion into exon 11 causes premature termination of the reading frame at the position of the 348th amino acid in the CYP3A5*7 allele, thus producing unstable CYP3A5 proteins. Similar to CYP3A5*6, it is found only in populations of African origin (Zimbabwean, 10% and African-American, 10%), not in Caucasian and Asian populations.[22] The CYP3A5*8 variant, presenting a substitution of nucleotide C to T, leads to an amino acid change from arginine to cysteine at codon 28.[13] It was first observed in African-American (4%), but the frequencies in other ethnic groups have not yet been revealed. CYP3A5*9 is a SNP in the coding region, resulting from a nucleotide substitution from G to A in exon 10, leading to an amino acid change from alanine to threonine at codon 337. It was observed in an Asian population at a frequency of 2%.[13] CYP3A5*10 was identified in one American subject out of a group of 24 diverse Caucasians, with an allelic frequency of 2%.[10] It is a point mutation substituting T to C in exon 12, resulting in an amino acid change at residue 446 from phenylalanine to serine.[10]

In vitro data showed that CYP3A5*1 exhibited the highest maximal clearance for testosterone and the highest V_{max} (maximal capacity) for nifedipine oxidation, followed by CYP3A5*9, CYP3A5*8, and CYP3A5*10.[23] In particular, the report also showed that subjects with CYP3A5*10 exhibited a greater than 95% decrease in the intrinsic clearance for both nifedipine and testosterone metabolism.[23]

Clinical implications of CYP3A5 polymorphism

Hypertension

The CYP3A enzymes metabolize cortisol into 6β-hydroxycortisol, and corticosterone into 6β-hydroxycorticosterone.[24,25] It was shown that the levels of 6α-hydroxycortisol and 6β-hydroxycorticosterone were higher by an average of 48% in patients with essential hypertension compared to normotensive subjects. Ho et al. reported that the participants with hypertension had a greater occurrence of hypertension, or are involved in blood pressure control. Rais et al. reported an association between the urinary 6β-hydroxycortisol/cortisol ratio and the CYP3A5 genotypes in a North Indian normotensive population, and showed the mean 6β-hydroxycortisol/cortisol ratios to be 110, 76 and 69 in wild-type CYP3A5*1/*1 (n=12), CYP3A5*1/*3 (n=62) and CYP3A5*3/*3 (n=76), respectively, suggesting a substantial role of the polymorphic CYP3A5 genes in the disposition of steroid hormones.[27] Ho et al. reported that the participants of African origin with CYP3A5*3/*3 (146±35 mm Hg) had a higher systolic blood pressure than those with the CYP3A5*1/*3 (119±14.1 mmHg; P=0.0006) and CYP3A5*1/*1 (125±17.4 mmHg; P=0.009) genotypes, but no association was detected between CYP3A5 genotype and blood pressure in Caucasians.[28] They concluded that although blood pressure may be higher in untreated participants of African origin possessing the CYP3A5*3/*3 genotype, the CYP3A5*1 allele may be associated with hypertension that is more refractory to treatment in this ethnic group. However, the current data on the association between CYP3A5 polymorphisms and hypertension or blood pressure control show inconsistencies.[29]
Cancer

CYP3A5 is primarily expressed in the liver and the gastrointestinal tract, and metabolizes endogenous compounds including the steroid hormones testosterone and progesterone, and fatty acids. Based on the assumption that CYP3A5 plays a role in the modulation of steroid hormone levels, many scientists have evaluated the role of CYP3A5 polymorphisms in cancer risk, including in the following cancers: acute or chronic leukemia, prostate cancer, colorectal cancer, gastric cancer, esophageal cancer, testicular cancer, and breast cancer. A recent meta-analysis revealed that CYP3A5*3 polymorphism may increase the risks of acute leukemia, chronic leukemia, and colorectal cancers. However, no evidence was found of association in prostate cancer, liver cancer, and other cancers with CYP3A5*3 polymorphisms. Additionally, the finding was more striking among Asian and Caucasian populations, suggesting ethnic differences in the occurrence of cancers.

Other diseases

Feng et al. studied the role of both CYP2C19*3 and CYP3A5*3 polymorphisms in the susceptibility of Chinese pediatric tuberculosis patients to disease, and found both genetic polymorphisms contributed to protection from tuberculosis. They speculated that this was attributed to the reduction of intracellular M. tuberculosis, caused by successful apoptosis under the influence of reactive oxygen species (ROS) through these genetic polymorphisms.

Du et al. assessed the genetic susceptibility to schizophrenia in association with the CYP3A4/3A5 genes, and concluded that CYP3A4*1G and CYP3A5*3 polymorphisms were strongly associated with the occurrence of schizophrenia. Alterations in dopamine and serotonin (5-HT) levels in the brain have been implicated in the etiology of psychiatric diseases, including schizophrenia and depression. Accordingly, these molecules have been targeted for pharmacotherapy in the field of psychiatry. Cytochrome P450s, including CYP1A1, 1A2, 3A4, and 3A5, are involved in serotonin metabolism, and messenger RNA of both CYP3A4/3A5 is expressed in the brain. These findings indicate that CYP3A5 may play a crucial role in the disposition of dopamine and serotonin in the brain, thereby causing the possible associations of polymorphic expression with the psychiatric diseases, including schizophrenia.

Tobacco smoke contains polycyclic aromatic hydrocarbons (PAHs), which become activated in the body by action of the cytochrome P450s. Based on the assumption that the activated PAHs are associated with decreased lung function, for which CYP3A5 is one of the PHA-metabolizing enzymes, Kaur-Knudsen et al. studied whether CYP3A5*3 influences lung function and the risk of chronic obstructive pulmonary disease (COPD) in smokers. However, no association could be identified in the study between CYP3A5*3 and decreased lung function or risk of COPD among those who have smoked.

Pharmacokinetics of CYP3A substrates

The CYP3A enzymes have very broad substrate specificity, and an extremely large number of structurally diverse drugs are metabolized by a variety of different pathways through the enzymes. Considering that CYP3A enzymes including CYP3A5 participate in the biotransformation of 50% of the pharmaceutical drugs currently in use, it is obvious that the polymorphic CYP3A5*3 gene must play a crucial role in the pharmacokinetics of these CYP3A substrates. It is reasonable to assume that polymorphisms in the CYP3A5 gene should lead to interindividual variability, which has been observed in the pharmacokinetics of CYP3A substrates. Similar to other studies evaluating the role of CYP3A5*3 polymorphism, when we assessed the effect of CYP3A5*3 polymorphism on the pharmacokinetics of various CYP3A substrates, we found increased drug exposure or plasma drug levels for the following: simvastatin, amlodipine, risperidone, and carbamazepine. In the case of alprazolam, after a 1 mg dose was administered to healthy individuals, the area under the plasma concentration-time curve (AUC) for alprazolam was significantly greater in subjects with the CYP3A5*3/*3 polymorphism (830.5 ng*h/mL) than in those with CYP3A5*1/*1 (599.9 ng*h/mL) (P=0.030), while the oral clearance was also significantly different between the CYP3A5*1/*1 (3.5 L/h) and CYP3A5*3/*3 groups (2.5 L/h) (P=0.036). Simvastatin also showed similar results: after 20 mg simvastatin medication in healthy subjects, the AUC in the CYP3A5*1/*1 carriers (4.94 ng*h/mL) was significantly lower than in the CYP3A5*3/*3 carriers (16.35 ng*h/mL; P=0.013). The oral clearance was also significantly different between CYP3A5*1/*1 carriers (4.80 L/h) and CYP3A5*3/*3 carriers (1.35 L/h; P<0.005). Besides these studies, many scientists have evaluated the role of CYP3A5*3 polymorphisms in the pharmacokinetics of various CYP3A substrates.

Despite the clear evidence that the polymorphic CYP3A5*3 gene leads to decreased enzyme activity, intriguingly, a contradictory finding showing a higher clearance in subjects with the CYP3A5*3 allele than those with normal allele was also observed. In the case of amiodipine, the oral clearance was lower in the CYP3A5*1 carriers (27.0 L/h) than the CYP3A5*3/*3 (32.4 L/h) carriers (P=0.063), but the mean AUC of amiodipine was higher in the CYP3A5*1 (200.9 L/h) carriers than in the CYP3A5*3/*3 (167.6 L/h) carriers (P=0.029). This finding indicates that despite the molecular evidence that CYP3A5*3 has a dysfunctional enzyme activity, the CYP3A5*3 enzyme can still have a higher activity than the CYP3A5*1 enzyme for some CYP3A substrates; however, the mechanism(s) for CYP3A5*3 carriers to exhibit a higher clearance rate than normal CYP3A5*1 carriers could not be clearly explained. Another recent study also observed consistent findings to ours when investigating amlodipine pharmacokinetics.

Conflict of Interest

Nothing to declare
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References


42. Shimada T, Martin MV, Puress-Schwart D, Marnett LJ, Guengerich FP. Roles of individual human cytochrome P450 enzymes in the bioactivation of benzo(a)pyrene, 7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene, and other dihydrodiol derivatives of polycyclic aromatic hydrocarbons. Cancer Res


