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Unveiling the Enigmatic CYP3A4 Enzyme : A Literature Review

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ABSTRACT

Cytochrome P450 3A4 (CYP3A4) is a crucial enzyme in the human body, primarily responsible for endobiotic and xenobiotic metabolism, including many commonly prescribed medications. It plays a pivotal role in the biotransformation of more than 50% of drugs. But the high frequency of genetic polymorphisms in the CYP3A4 gene contributes to significant interindividual variability in enzyme activity. These genetic variations can affect drug metabolism rates, leading to altered pharmacokinetics and necessitating dose adjustments for certain medications, particularly in populations with different allele frequencies. The impact of these genetic variants can vary significantly across different ethnicities, highlighting the importance of pharmacogenetic testing in personalized medicine. However, there is currently a lack of a comprehensive study examining this variability across different ethnicities. This review will help understand these genetic differences across population and ethnicity to allow healthcare providers to tailor drug therapies to individual genetic profiles, enhancing treatment efficacy and safety.
Keyword: CYP3A4, enzyme, star allele, variation, ethnic

ABSTRAK

Sitokrom P450 3A4 (CYP3A4) merupakan enzim dalam tubuh manusia yang bertanggung jawab dalam metabolisme endobiotik dan xenobiotik, termasuk obat-obatan yang sering diresepkan. Enzim ini diketahui berperan penting dalam biotransformasi lebih dari 50% obat yang beredar di pasaran. Namun, tingginya frekuensi polimorfisme genetik pada gen CYP3A4 berkontribusi signifikan terhadap aktivitas enzim tersebut. Variasi genetik ini dapat memengaruhi laju metabolisme obat, sehingga menyebabkan perubahan farmakokinetik, dan pada akhirnya juga mempengaruhi efektivitas obat. Dampak dari varian genetik ini juga ditemukan bervariasi secara signifikan pada etnis yang berbeda, sehingga menjadi dasar pentingnya uji farmakogenetik. Namun, studi komprehensif yang meneliti variabilitas ini di berbagai etnis cenderung minim. Ulasan ini akan membantu memahami variasi genetik CYP3A4 di seluruh populasi dan etnis untuk memungkinkan penyediaan layanan kesehatan yang menyesuaikan terapi dengan profil genetik individu, sehingga dapat meningkatkan efektivitas dan keamanan pengobatan.
Kata kunci: *CYP3A4, enzim, alel bintang, variasi, etnis*

1. Introduction

CYP3A4 is regarded as the most prominent human enzyme in drug metabolism because it is responsible for metabolizing 50% of medicinal drugs [1,2]. The liver is the primary site of expression for CYP3A4, accounting for around 14.5% to 37% of the total hepatic pool. Furthermore, CYP3A4 is the predominant CYP enzyme found in the cell lining of human intestines. The presence of intestinal CYP3A4 enzymes affects the

bioavailability of some drugs, which undergo first-pass metabolism before being absorbed into the body [2,3,4].

Chemotherapy medications and opioids are examples of drugs that are metabolized to some extent by CYP3A4. Researchers have identified CYP3A4 as a crucial factor in determining the effectiveness of these substances and the patient's reaction to them [5]. Tamoxifen, zolpidem, erythromycin, prednisolone, carbamazepine, nifedipine, and loratadine are more examples of drugs that are metabolized by CYP3A4 [6]. CYP3A4 is also crucial in the metabolism of endobiotics such as bile acids and steroids. It specifically catalyzes the process of 1β-hydroxylation of the secondary bile acid deoxycholic acid. CYP3A4 also breaks down cholesterol, producing a metabolite in the process [5].

2. Dimensional Structure of CYP3A4

The structure of CYP3A4 is characterized by its dynamic and intricate nature. As a holoenzyme, it remains a composite of an apoenzyme and a prosthetic group. The CYP3A4 apoenzyme is a globular protein with a mostly alpha-helical structure. The structure will start with a small beta-strand N-terminal domain, followed by a broader, helical C-terminal domain. CYP3A4 possesses a total of 12 alpha helices, which are denoted as A-L and arranged in sequential order from the closest to the N-terminal. The C-terminal domain of CYP3A4 houses both the heme and the active site [7,8].

A conserved cysteine (Cys 442) flanks the heme iron in helix I, while the heme propionates interact with the side chains of Arg 105, Trp 126, Arg 130, Arg 375, and Arg. The solvent can reach the heme through channels created by beta sheet 1, the B-C loop, and the F-G area [8]. Substrate binding most significantly impacts the B', E, and K' helices of CYP3A4. Curiously, when a substrate is bound, the C helix, which is involved in the binding of Cytochrome P450 Reductase (CPR), also experiences increased rigidity. The results suggest that CPR and substrates may work together to change the dynamic structure of CYP3A4 and the way they bind to each other [9].

The CYP3A4 binding pocket's estimated ligand-accessible volume is 520 A, indicating a significant size. The flexibility of CYP3A4 is widely known as a key factor in its exceptional ability to recognize and bind to many compounds. Furthermore, the CYP3A4 binding pocket can also adopt numerous conformations [5].

Researchers have used a variety of techniques to examine the extensive binding of substrates to CYP3A4, leading to the following findings:[10]

- At different stages of the catalytic cycle, substrates in the CYP3A4 active site can dissociate and rebind.
- A loose fit allows another substrate in the active site to influence the binding affinity and turnover of one substrate.
- Substrate association may involve a step that does not cause changes in the heme spectrum, making it undetectable by absorbance spectroscopy (referred to as 'absorbance-silent').
- Prior to entering the active site cavity, CYP3A4 ligands have the potential to interact with a peripheral binding site. There is ongoing debate over whether the presence of several substrate binding conformers or the existence of kinetically distinct mechanisms, specifically the 'induced fit' and 'conformational selection' mechanisms, is the primary cause of unusual reaction rates.

The structure of CYP3A4 exhibits several distinctive characteristics compared to other P450 enzymes. In the loop, there is a distinct hydrophobic region that comes after helix A", which is a helix that has not been seen in previous P450 crystal structures. This area, along with the hydrophobic G' helix and the loop that connects the G' and G helices, could make it easier for the protein to interact with the microsomal membrane. The additional surprising characteristic of the CYP3A4 structure is the region that comes after helix F. This helix's length is significantly shorter than that of other P450 structures. It forms a well-organized region of the polypeptide chain that does not follow any specific secondary structure pattern. The region in question is situated superiorly and at a right angle to helix I. It encompasses several residues that have been demonstrated, using site-guided mutagenesis, to play a direct or indirect role in the functioning of CYP3A4 [8].

3. CYP3A4 Gene and Its Regulatory

The genes responsible for encoding CYP3A enzymes are situated on the 7q21–q22.1 chromosome band, together with CYP3AP1 and CYP3AP2 pseudogenes. A cluster of these genes spans approximately 231 kilobases. Therefore, all CYP3A isoform enzymes have a notable level of structural similarity, ranging from 71.5% to 84.1% and are composed of 13 exons [2,11].

The 5’ untranslated region (UTR) of each human CYP3A gene has an average length of 101 nucleotides, which is shorter than the average length of 150 nucleotides for the 5’ UTR in humans. In contrast, the length of the 3’ untranslated region (UTR) varies significantly, with CYP3A5 having 111 nucleotides, CYP3A7

having 463 nucleotides, CYP3A43 having 549 nucleotides, and CYP3A4 having 1152 nucleotides. UTRs play a crucial role in gene expression control. Thus, due to its longer 3' UTR, CYP3A4 is likely to be subject to significant regulation.The arrangement of the CYP3A locus suggests that it originated from the replication of an ancestral CYP3A [11].

The length of the CYP3A4 gene plus its 5' flanking region is 27,592 base pairs, and it contains a coding region consisting of 13 exons. A basal transcription element, an AP-3 binding site, a p53 binding motif, a hepatocyte nuclear factor-4 (HNF-4) element, two hepatocyte nuclear factor-5 (HNF-5) elements, a glucocorticoid response element (GRE), a pregnane X receptor element (PXRE), and an estrogen response element are all found in the promoter region. The protein produced by gene transcription is composed of 502 amino acids and has a weight of 57.29 kDa. This makes it the largest CYP enzyme found in humans. The protein is characterized by a complex arrangement of helices and sheet structures [12].

The constitutive regulation of CYP3A4 transcription, both positive and negative, is controlled by hepatocyte nuclear factor (HNF4) and other hepatic transcription factors, such as HNF1 and HNF3, CCAAT/enhancer-binding proteins alpha and beta (C/EBP and C/EBP), and upstream transcription factor 1 (USF1). These factors connect to three main cis-acting modules: the constitutive liver enhancer module 4 (CLEM4), which is located between 11.4 and 10.5 kbp; the distal xenobiotic-responsive enhancer module (XREM), which is located between 7.2 and 7.8 kbp; and the proximal promoter (prP) [3,11,13].

Xenobiotics and endobiotics induce CYP3A4 through an indirect process that involves activation of specific ligand-dependent nuclear receptors. There are a number of these receptors, such as the glucocorticoid receptor (GR), the estrogen receptor (ER), the farnesoid X receptor (FXR), the liver X receptor (LXR), and the peroxisome proliferator-activated receptor alpha (PPAR). Additionally, the induction occurs through binding to three major cis-acting modules: CLEM4, distal XREM, and prPXRE [3,11].

PXR is considered the primary and essential determinant affecting the function and manifestation of the hepatic enzyme CYP3A4. After forming a complex with the ligand, PXR travels into the nucleus. Once it reaches that location, it forms a heterodimer with the retinoid X receptor (RXR), increasing the transcription of CYP3A4 by binding to AG (G/T) TCA-like direct repeats separated by either 3 or 4 bases (known as DR3 and DR4, respectively), as well as to everted repeats separated by 6 bases (referred to as ER6). The PXR and RXR proteins form a heterodimer that binds to the ER6 sequence in the proximal promoter, the DR3 sequence in XREM, the ER6 sequence in a distant enhancer module, and the DR4 motif. Ultimately, it will enlist co-activators and trigger CYP3A4 activation [11].

The activation of nuclear factor kappa B (NF-κB) mediates the suppression of CYP3A gene expression by interfering with the PXR-RXR complex binding to DNA. The proteins p53 and C/EBP-LIP also play a role in suppressing the function of the CYP3A4 gene. During the inflammatory response, the suppression of CYP3A4 transcription is effectively disrupted, and it is achieved through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, which is mediated by cytokines [14].

The cytokines IL-1, IL-6, and TNF significantly lower the expression of CYP3A4 and CYP3A5 in human liver cells, as well as on the CYP3A genes in mouse and rat liver cells. IL-6 appears to have a crucial role in reducing the activity of CYP3A enzymes during inflammation. This is achieved through the involvement of the glycoprotein receptor gp130 and the C/EBP signaling pathway [11].

Epigenetic factors such as DNA methylation, histone modifications, and noncoding RNA regulation also influence the expression of CYP genes. Modifications to histone proteins after translation, including acetylation, methylation, phosphorylation, ubiquitination, and others, have the ability to modify the structure of chromatin and the ability of DNA to be transcripted, thus impacting gene expression. For example, histone modifications may be involved in the alterations of CYP3A4 and CYP3A7 expression during the embryonic period and the first two years after birth. This pathway appears to be significant for CYP3A4 [11,15].

DNA methylation at CpG sites inside a promoter region suppresses gene transcription and has multiple impacts on the expression of CYP genes in different organs. As an illustration, 5-aza-2-deoxycytidine, a methylation transferase inhibitor, enhances the levels of PXR and CYP3A4 expression in HepG2 cells. This effect is dependent on both the concentration and duration of treatment. In contrast, the process of methylation on a CYP3A4 enhancer hinders the PXR-mediated transcriptional activity of CYP3A4 and prevents the binding of PXR to the CYP3A4 promoter. As a result, rifampicin ceases to stimulate CYP3A4 expression due to methylation of the CYP3A4 promoter and enhancer [11].

Noncoding RNAs, specifically miRNAs and lncRNAs, have been recognized as epigenetic regulators of CYP gene expression. Non-coding microRNAs can regulate CYP3A at both the transcriptional and post-transcriptional levels through two distinct mechanisms: either by directly interacting with the 3'-untranslated region (3'UTR) of the CYP3A4 mRNA or by binding to the 3' UTR mRNA of nuclear receptor genes that are

responsible for regulating the CYP gene. In doing so, it can influence the activity of CYP3A4 activators or repressors [15].

After the transcription process, changes in the amounts of miR-150-5p, miR-27b, and miR-200a-3p have been shown to lower CYP3A4 activity. Similarly, miR-34a, miR-30c-1-3p, and miR-27b affect the functioning of RXRa, PXR, and VDR [15].

It has been shown in several lab tests that miR-27b binds directly to the 3'-untranslated region (3'-UTR) of CYP3A4 and lowers the production of CYP3A4 protein. In humans, the amount of miR-27b in the blood is negatively related to the activity of CYP3A4. This implies that miR-27b could serve as a valuable biomarker. Additionally, miR-27b interacts with VDR, which results in a decrease in the expression of the CYP3A4 protein [16].

In addition to endogenous and exogenous influences, inter-individual variances also contribute to the diversity of CYP3A4 expression and function. Interindividual variations arise from a multitude of causes, including genetic polymorphisms, age, sex, diseases, medicines, and environmental toxins. Genetic variations play a significant role in the differences between individuals in terms of CYP3A expression and function [16].

4. CYP3A4 Structure-Activity Relationship and Their Impact

Thus far, around forty non-synonymous genetic variants of CP3A4 have been discovered. The CYP3A4*1 allele category's wild type is the CYP3A4*1A-T subtype, as stated in the latest version of the CYP3A4 allele nomenclature database. The CYP3A4*2 to *26 alleles are located in the exons and have been demonstrated to modify protein sequences, except for CYP3A4 *18B and *22, which are situated in the intron [17].

Several studies suggest that the frequency of allelic variants CYP3A4*2, CYP3A4*7, CY3A4*16, and CYP3A4*18 ranges from 1.4% to 3% in Caucasian populations and from 1.3% to 5% in Japan. Studies conducted both in laboratory settings (in vitro) and in living organisms (in vivo) have demonstrated that these genetic variants exhibit different levels of metabolic activity. These variations are one of the mechanisms contributing to the differences in how individuals metabolize endobiotics and xenobiotics [18]. Below is a comprehensive list of several CYP3A4 star alleles, along with their structural variants and the specific drugs that they affect.

Table 1. CYP3A4 star allele summary

Allele (nucleotide change)	Location	Structural Change	Activity	Affected Drug	References
*1B (rs2740574, - 392A>G)	Promoter	x	↓	Cyclosporin A (higher C0/D)	[19]
*4 (rs55951658,352 A>G)	Exon	I118V	↓	Simvastatin (lower TG) Anandamide (lower anandamide metabolite)	[20], [21]
*12 (rs45614732,1117 C>T)	Exon	L373F	↓	Quinine (lower Cl_{int})	[22]
*16 (rs12721627,554 C>G)	Exon	T185S	↓	Midazolam Carbamazepine Quinine (lower Cl_{int})	[22], [23]
*18B (rs2242480, 82266 G>A)	Intron	x	↑	Cyclosporin (lower Cmax)	[24], [25]
*20 (rs67666821, 1461_1462 insA)	Exon	488 frameshift	↓	Midazolam Quinine (lower Cl_{int})	[22], [26]
*22 (rs35599367, 15389 C>T)	Intron	x	↓	Tamoxifen (higher tamoxifen/NDM) Pazopanib (lower Cl_{int})	[27], [28]

5. Race/Ethnicity-Related CYP3A4 Polymorphism

Race/ethnicity significantly influences the variation of CYP3A4 activity, influencing the processing of drugs and xenobiotics, the response to them, and the potential for toxicity. The extent of interracial diversity in CYP activity has been thoroughly investigated for certain enzymes. It is frequently associated with disparities in nutrition, physiology, and the prevalence of genetic variations [29,30].

Different racial and ethnic groups exhibit notable variations in CYP450 activity. Inter-racial variability in the activity of CYP3A4 is relatively unknown, despite the enzyme's therapeutic role [30,31]. One of the pioneering investigations in Mexico used oral felodipine to substantiate this hypothesis. Felodipine, a dihydrophyridine-class drug, is a calcium entry channel inhibitor that is prescribed for hypertension and pulmonary angina disorder. CYP3A4 is the primary enzyme involved in the biotransformation of felodipine. The bioavailability of felodipine in Mexican patients is substantially different from that of Canadian, Swedish, and Danish subjects. This finding suggests that a higher level of felodipine in the Mexican population may be the result of decreased CYP3A4 activity when compared to Canadian, Swedish, and Danish respondents [32].

Another study suggests that the CYP3A4*1B polymorphism could be responsible for the differing racial and ethnic variability in CYP3A4 metabolism. The CYP3A4*1B polymorphism's A > G transition is located at the -392 position of the gene promoter region. African Americans (35–67%), Hispanic Americans (9.3–11%), Chinese and Taiwanese (0%), and Caucasians (2–9.6%) are the ethnic groups with a higher prevalence of CYP3A4*1B [29].

The recently identified CYP3A4*20 is another potential polymorphism that could account for variations in CYP450 activity among various racial and ethnic groups. African Americans (26%), Chinese (22%), and Caucasians (6%), among other ethnic groups, exhibit a relatively high prevalence of this recently identified SNP [26]. Another SNP in intron 6 of CYP3A4, CYP3A4*22, was identified and exhibited reduced expression in vitro. Carriers of the CYP3A4*22 polymorphism enhance simvastatin-mediated cholesterol reduction, which is associated with reduced necessary statin doses (allele frequencies of 4.3, 4.3, and 8.3% for African Americans, Chinese, and Caucasians, respectively) [33].

Another report explains why healthy, age-matched men of South Asian descent had significantly superior midazolam clearance compared to those of Caucasian descent. In this regard, Caucasians demonstrate a higher prevalence of the primary reduced function mutation (CYP3A4 *22) than other ethnic groups. In this investigation, the CYP3A4 (*1/*22) genotype was less prevalent in the South Asian population. Therefore, it is logical that participants who identified as South Asians exhibited a higher midazolam clearance than those who identified as Caucasian [31].

Furthermore, an additional investigation identified the most prevalent CYP3A4 variants within each ethnic group. The seven ethnic groups represented in this study are: European (non-Finnish), European (Finnish), Askhenazi Jewish, Latino, African, East Asian, and South Asian. The most prevalent alleles among European (non-Finnish), European (Finnish), Askhenazi Jewish, Latino, African, East Asian, and South Asian individuals are rs4986908/*10 (C>G), rs55785340/*2 (A>G), rs748236460 (T>C), rs19908125 (C>T), rs12721629/*12 (G>A), rs28371759/*18 (A>G), and rs568779023 (C>G), in that order [34].

Another study emphasizes that Asian ethnicities generally shared similar MAFs for CYP3A4 polymorphisms, despite the fact that African-American and European-American populations had distinct MAFs (minor allele frequencies). Pharmacogenetic markers detected the MAFs of CYP3A4*1B (rs2740574) in European Americans (0.042) and African Americans (0.271). However, the polymorphism was not detected in any Asian populations [35].

This study had also identified CYP3A4*18 (rs28371759) as the other pharmacogenetic marker responsible for bidirectional enzyme activity.35 Previous studies have demonstrated that the polymorphism slows down the metabolism of nifedipine and midazolam, while speeding up the metabolism of testosterone and chlorpyrifos.36,37 Furthermore, prior research indicates that Asian populations, including Chinese (0.008–0.01), Japanese (0.013), Koreans (0.012–0.017), and Malaysians (0.021), frequently exhibit the presence of CYP3A4*18. The current investigation revealed the polymorphism in two Asian populations: the Korean population, with a frequency of 0.021, and the Japanese population, with a frequency of 0.010 [35].

In a different study, the amounts of CYP3A4*18A T>C (rs28371759), CYP3A4*18B G>A (rs2242480), and CYP3A5*3 in Malaysians were found to be 0.03, 0.48, and 0.64, respectively. Nevertheless, neither CYP3A4*4 A>G (rs55951658) nor CYP3A4*22 C>T (rs35599367) alleles were identified. The findings indicate a high prevalence of the CYP3A4*18B G>A variant among Malaysian individuals [30]. Therefore, further investigation is necessary to gain a more comprehensive and enhanced understanding of the mechanism behind the impact of racial and ethnic factors on CYP3A4 expression and activity.

6. Conclusion

This review suggests that the frequency of CYP3A4 variant alleles varies significantly across ethnicities and also affects enzyme activity variability. Understanding the ethnic differences in CYP3A4 allele frequencies is crucial for personalized medicine, as it can help predict drug metabolism and guide dosing recommendations based on an individual's genetic profile. Ethnicity-based classification of CYP3A4 polymorphisms is a step towards precise medicine tailored to an individual's genetic makeup.\

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