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Review

CYP2D6 pharmacogenomics

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ABSTRACT

Cytochromes are proteins that catalyze electron transfer reactions of many metabolic pathways. They are involved in drug metabolism and thus determines the therapeutic safety and efficacy of drugs in patients. Cytochrome P450 in mitochondria accounts for 90% of the oxidative metabolism of clinically used drugs during phase 1 reaction. CYP2D6 is a major gene member of this superfamily as it carries out metabolism of 25% of drugs currently available in the market. Contrary to the concept of specificity of enzyme action these can metabolize substrates of different chemistry. Since its discovery, many have intensively studied this unique hemoprotein and contributed to the elucidation of its molecular properties and physiological functions and also the structure-activity relationships of its substrates and inhibitors. Its activity ranges considerably within a population due to genetic polymorphisms which lead to varied responses to drug intake. Studying such polymorphisms which cause a significant impact in the management of patients and helps to achieve the final target of personalizing medicine. This review briefs about history, structure, and function, molecular genetics, substrates, regulators and inhibitors of CYP2D6 and its clinical pharmacogenomics.

Contents

1. Introduction

The ability to metabolize drugs is a natural process which involves the same enzymatic pathways and transport systems that are used for normal metabolism of dietary constituents. They are called xenobiotic metabolizing enzymes. Drugs which are lipophilic need to be changed into water soluble compounds for excretion from the body, if not leads to accumulation and toxicity. This process happens via chemical reactions which involve two phases; phase 1 and 2. The enzymes for these are found in most tissues in the body with the highest levels located in the gastrointestinal tract (liver, small and large intestines). Other sites are kidney, breast, brain and lungs. Intracellular membranes and cytosol of cells contain these enzymes. These enzymes are pigments (cytochromes) as they contain haem and are found in all organisms in the prokaryotic and eukaryotic world from animals, plants, fungi, protists, bacteria and archaea to virus. There are different types of cytochromes of which cytochrome P450 is unique in its drug metabolizing function. Genetic variation in their genes leads to a varied response to drug intake. Three families of CYPs (Cytochrome P450), namely CYP1s, CYP2s, and CYP3s are the main ones

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contributing to the oxidative metabolism of more than 90% of clinical drugs [1]. CYP2D6 is one of the most widely investigated CYPs. 25% of currently marketed drugs are substrates for CYP2D6 though it only constitutes 2–4% of the total hepatic CYPs [2]. Its substrate includes antidepressants, antipsychotics, analgesics, antitussives, β-blocking agents, antiarrhythmics, and antiemetics and thus its different drug metabolism affects the clinical outcome.

2. History of cytochrome P450

In 1885 Dr.Mac Munn discovered two new pigments in animals, which he named as myohaemetin and histohaemetin and published it in the Proceedings of Physiological Society, Royal College of London. He mentioned them as respiratory pigments as they undergo oxidation and reduction in solid organs without getting destroyed. Later in 1929 David Keilin an entomologist while studying the life cycle of horse bot fly noticed red pigments in its larvae that feed on a horse. He got interested about animal pigments that led further research in this field. In his article about respiratory enzymes, he named the pigments as cytochromes and explained the different types of cytochromes based on their position in the absorption band as cytochromes *a* (605 nm), b (565 nm) and c (550 nm) [3]. Klingenberg in 1955 discovered a new carbon monoxide binding pigment in rat liver microsomes at Johnsonn Research Foundation, Philadelphia [4]. He reduced microsomal suspension compounds by adding DPNH (DiPhosphopyridine Nucleotide) and studied its spectra using wavelength-scanning recording spectrophotometer and observed a prominent optical absorption peak at 450 nm. This absorption spike was different from other haem proteins which usually show CO (Carbon Monoxide) difference spectra between 500 and 650 nm. Aerated microsome suspension when bubbled with CO didn't show any peak indicating that P450 is a reducible pigment, and only the reducible form could bind CO. Omura et al. repeated Klingenberg's experiments using rabbit liver microsomes and found similar results in its absorption spectra [5]. He named the pigment as P450 where P stands for "pigment". When treated with detergents the absorption peak at 450 disappeared, and a parallel peak appeared at 420 nm which was due to the formation of a more solubilised P420. Spectral data of P420 helped in finding the molar attenuation coefficient of carbon monoxide difference spectrum of P450. Thus they could calculate the amount of P450 in the microsomes, and the total content of protoheme was accountable by the sum of cytochrome b5 (a ubiquitous electron transport hemoprotein) and P450. This 450 peak is shared only by four classes of haem proteins, others being nitric oxide synthases, chloroperoxidases, and protein H450. Thus they were grouped under enzymes which help in oxidation and reduction.

3. Human CYP2D6; structure and function

The purification of the CYP enzymes was done with chemical stabilization techniques developed by Ichikawa et al. and Coon et al. in 1969 [6]. The primary structure of the protein (high-resolution crystal structure) was elucidated in Pseudomonas putida in 1982 [7]. CYPs are embedded in the phospholipid bilayer of endoplasmic reticulum in the cytosolic surface. Enzyme called NADPH-CYP450 oxidoreductase seen close to CYP transfers electrons to all forms of cytochromes. Each CYP contains one molecule of iron-protoporphyrin IX which binds with oxygen and a non-covalently bound polypeptide chain. The detailed study of the structure revealed two conformations; open and closed. These symmetries are important as switching between them is needed for substrate access to the active site. Most of the P450s share the form change of closed to the partly open configuration. The active site of drug metabolizing cytochromes adapts to several substrates which explain the multi-drug metabolizing properties of several cytochromes. Active site cavity of CYP2D6 is bordered by the haem and lined by many amino acid residues and is of 540 A^3 (Angstrom) size which can accommodate a number of substrates with distinct structures [8]. The entry to the active site is obscured while in closed form, but the access channel undergoes a significant increase in thermal motion which shows that fluctuations do occur to allow a substrate to reach the active site. Four amino acids are conserved in the 57 functional CYPs; Glu-242 (Glutamate), Arg-245 (Arginine), Phe-310(Phenylalanine) and Cys-316 (Cysteine) of which phenylalanine and cysteine are seen near heme binding region.

It was aware that carbon monoxide inhibited the metabolism of steroids in experimental studies. Detailed study of this inhibition using photochemical action spectrum method found that cytochrome P450 is also present in mitochondria and is involved in the synthesis of steroids helping in hydroxylation of 17α hydroxyprogesterone. Carbon monoxide competes with molecular oxygen for the active site of P450 as it acts as the oxygenase for the hydroxylation step. Estabrook and Omura worked together to find the actual mechanism of reactions involving P450 and first elucidated P450 enzyme electron transfer in 1966 [9]. The electron has to flow through NADPH-linked soluble flavoprotein and a non-haem iron protein to reduce P450 and which in turn reacts with oxygen and substrate in which one atom of oxygen is used to reoxidize itself and other to hydroxylate the substrate. This oxidation process consumes more oxygen compared to substrate metabolized in the reaction resulting in the generation of free radicals that become water by the action of superoxide dismutase. CYPs are involved in the phase 1 reactions of drug metabolism like aromatic hydroxylation, N-oxidation, N-dealkylation, O-dealkylation, S-oxidation, deamination, and dehalogenation. CYPs also catalyze many unusual reactions such as one-and-two-electron reductions, one-electron oxidation, oxidation cleavage of carboxylic acid esters, desaturation, deformylation of aldehydes, ring formation, ipso mechanisms of aryl dehalogenation and O- and N- dearylation, rearrangements of oxidized eicosanoids, aldoxime dehydration and hydrolysis of phosphatidyl choline. The estimated half-life of human CYP2D6 is 46.6 to 51 h [10]. Any factors which change the stability and degradation of human CYPs will change their half-life and thus modify the drug metabolism.

4. Molecular genetics of CYPs

Modern P450s originated from an ancestral gene in prokaryotes that existed approximately 3.5 billion years back, before the advent of eukaryotes and the existence of oxygen-rich atmosphere and they functioned as nitroreductases and endoperoxide isomerases. When earth's atmosphere started to accumulate oxygen, then CYPs protected early life forms from oxygen toxicity. This evolution happens by the process of repeated rounds of expansion of CYPs by gene duplication, exon shuffling, expression of overlapping genes, programmed frame shifting, alternative splicing, RNA editing and gene sharing. Around 1.5 billion years ago some of these expansions gave rise to endogenous compound metabolizing genes, and the last xenobiotic metabolizing expansion occurred around 400 million years ago. CYPs are phylogenetically, one of the most rapidly evolving genes, which is a characteristic that is needed to protect the cells from injuries when exposed to increasing toxic xenobiotic compounds. Genomic sequencing of cytochrome P450 s (CYPs) found that there are around 57 functional genes and 58 pseudogenes related to its synthesis in humans [11]. It belongs to a multigene family and encodes proteins with amino acid sequence identities >40%. Subfamilies include related proteins

with amino acid sequence matching >70%. There are 18 families and 43 subfamilies in human CYPs. The families are named CYP1, 2, 3, 4, 5, 7, 8, 11, 17, 19, 20, 21, 24, 26, 27, 39, 46 and 51. Among these families CYP2, 3 and 4 contain far more members than other 15 families. The biggest family in human CYP is CYP2 which includes 13 subfamilies and 16 functional genes. CYP genes often occur in clusters, with several related genes and pseudogenes. Psuedogenes are imperfect copies of genes that won't code for any proteins due to added up mutations by evolution but are seen near active genes. There are mainly 7 clusters related to CYPs; CYP2ABFGST, CYP2D, CYP2J, CYP3A, CYP4ABXZ, and CYP4F. CYP2ABFGST is one of the largest clusters and contains CYP2A6 and CYP2B6 genes. CYP2D cluster contains CYP2D6 gene [12]. Cytochrome families contain clans like the mitochondrial clan (first clan) that includes all the CYPs in the mitochondrial membrane. Others are 2, 3, 4, 7, 19, 20, 26, 46 and 51. Evolutionary evidence groups the families into clans; families within a single clan have likely diverged from a common ancestor gene. Functionally CYPs families are divided into two types; detoxification type (D type) and biosynthesis type (B type). Out of 57 genes, 35 are D-type genes, and 22 are B type genes. CYPs 1, 2, 3 and 4 are detoxification type CYPs. B-type genes are more conserved than D-type genes as proved by their psuedogenization rates; 0.2 vs. 6.9 per 100 million years, .i.e. disappearance of B type genes is around 30 times less than that of D type genes by mutation [13].

Human CYP2D6 gene belongs to chromosome 22q13.1 and contains 12 exons. It is highly polymorphic. To date, more than 100 allelic variants and many sub-variants of the CYP2D6 gene have been reported. As a part of the evolution of our intellectual capability, we take restricted food items that have resulted in the loss of a selection pressure to keep genes active. Thus human beings carry only one functional CYP2D6 gene whereas rat harbours 6 and mouse have nine functional genes. Evolution of human CYP2D locus has involved removal of three genes, inactivation of two (CYP2D7P and 8P) and partial inactivation of one. It includes fully functional alleles, alleles with reduced function and null alleles. Phenotypically they are divided as Ultrarapid Metabolizers (UMs), Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) based on comparing the metabolic enzyme ratio of substrate drugs and composes approximately 3–5%, 70–80%, 10–17% and 5–10% of Caucasians respectively [14]. The final phenotypic activity depends on the highest functioning allele; a person having EM allele and PM allele expresses EM phenotype. PMs having two non-functional alleles are seen in 19% of African Americans, 1% Chinese population and 0.6% of South Indian population [15]. They are at increased risk of adverse effects due to increased plasma level of the parent drug. UM, phenotype due to an additional functional gene is seen in 2% of Swedish Caucasians and 16% of black Ethiopians. IMs have two reduced functional or one reduced functional and non-functional allele. There is wide variability in allele distribution among different ethnic groups resulting in a variable percentage of metabolizers. PMs are mainly found in Europe, UMs are present in North Africa and Oceania, IMs are primarily located in Asia. There are around 109 different CYP2D6 variant alleles (1*B through *109), and around 507 SNPs of which 10% are nonsynonymous, that affects the protein structure. These variants result from point mutations, deletions or additions, gene rearrangements and duplication of the entire gene. *1A refers to the wild type or reference type haplotype.

5. Substrates of CYP2D6

CYP stands for cytochrome P450 superfamily, 2 is the family, 2D is the subfamily, and 6 is the member number. It is represented in other ways like – CYD6, CYP2D, CYP2D7AP, CYP2D7BP, CYP2D7P2, CYP2DL1, CYP11D6, P450C2D, P450DB1, CYP2D8P2, and P450-DB1. Other names for this enzyme are microsomal monooxygenase, xenobiotic monooxygenase, debrisoquine 4-hydroxylase. P450 can metabolize a large number of structurally diverse endogenous and exogenous compounds due to a broad substrate specificity and generally with a wide regio- and stereoselectivity. Substrates of CYP2D6 are usually lipophilic bases with a planar hydrophobic aromatic ring and a nitrogen atom that can be protonated at physiological pH and have a negative molecular electrostatic potential above the planar part of the molecule. The nitrogen atom is considered to be essential for electrostatic interactions with the carboxylate group of amino acids in the active site of CYP2D6. The prototypical substrates of CYP2D6 are debrisoquine and sparteine which are widely used to determine the phenotype of CYP2D6-mediated metabolism. Six SRS (Substrate Recognition Sites) are present in P450 which displays distinct differences in their substrate-binding residues. Molecular dynamics (MD) which combines statistical mechanics, classical mechanics, and intermolecular potential solves equations of actions for particles and can find the time-dependent atomic motions in CYP2D6 molecule following substrate binding. Propranolol is a lipophilic base with aromatic ring and nitrogen. Its interaction with cyp2d6 has been studied extensively. At first nanosecond following binding of propranolol Gly-218, Asp-301, Leu372, and Val374 change their location about propranolol by more than 2A which is shown by MD simulation [16]. The substrate binding cavity reorganizes by moving Glyc-218 and Leu-372 closer towards propranolol and Val374moves away from the substrate. Many of the TCAs, SSRIs, antipsychotics, hypnotics, opioids, antiemetics, antimigraine, *anti*-parkinsonism, antiarrhythmics, and beta blockers fits into the group of a substrate of CYP2D6.

6. Inhibitors of CYP2D6

CYP2D6 though is mostly non-inducible, is subjected to inhibition by many drugs and compounds that lead to drug-drug interactions. Strobl et al. in 1993 used a compound ajmalicine which is a potent inhibitor of CYP2D6 to find the structure- activity relationship of inhibitor group and found that a tertiary nitrogen atom which is protonated to higher degree at physiological pH and a flat hydrophobic region, with plane perpendicular to N–H axis and maximally extends up to a distance of 7.5A from the nitrogen atom is seen in inhibitors [17]. Elongation of alkyl chain dramatically increases the affinity of the compounds towards CYP2D6. The drug-drug interaction can be minor, mild or fatal. For example, CYP2D6 mediated venlafaxine-propafenone interaction may cause hallucinations and psychomotor agitation. Quinidine inhibits CYP2D6 mediated metabolic conversion of dextromethorphan thereby increase systemic bioavailability and less ADRs when used for pseudobulbar effect. The inhibitors can be irreversible inhibitors or reversible inhibitors. The irreversible inhibitors are cimetidine, paroxetine, pimozide, methamphetamine, metoclopramide, and desethylamiodarone. Some substrates and other compounds are found to inhibit CYP2D6 reversibly. Antipsychotics like olanzapine, chlorpromazine, fluphenazine, haloperidol, thioridazine, risperidone, clozapine, trifluperidol are metabolized by CYP2D6 and also significantly inhibit these enzymes. When co-administered with antidepressants like amitriptyline, imipramine, and fluoxetine, their plasma concentration will increase. H1 receptor antagonists like terfenadine, antifungal agents like terbinafine are CYP2D6 inhibitors. Usage of nortriptyline with terbinafine cause supratherapeutic drug levels in patients. Many protease inhibitors like ritonavir are potent inhibitors, and coadministration of ritonavir reduces the clearance of desipramine by 59%. Steroids like progesterone, testosterone are inhibitors and

are called atypical substrates as they lack basic nitrogen atoms. Lansoprazole, a potent inhibitor reduce the conversion of dextromethorphan to dextrophan. CYP2D6 metabolizes amphetamine analogs and they inhibit its action which can cause accumulation of drugs and toxicity. Many natural products like Panax ginseng, Ginkgo biloba inhibits CYP2D6 mediated debrisoquine metabolism.[18]

7. Regulators of CYP2D6

Cytochrome functions are regulated by internal and external factors at transcriptional, post-transcriptional, post-translational and epigenetic levels. CYP3A4 activity is higher in females, but clinical data on gender effects are conflicting in the case of CYP2D6 [19]. In general gender as a single factor only has a minor to moderate effect on CYP2D6 activity in humans. There is a positive correlation between postnatal age and increasing CYP2D6 activity; a gradual increase over the first year of life such that adult enzyme levels would not be achieved until approximately six months of age. Some studies have shown that there is a remarkably lower activity in >7 days to 18 years compared to adult value but could not find a convincing explanation for this. Mouse studies have found that activity and expression of the enzyme increases during pregnancy. Pregnancy is known to induce CYP2D6 mediated drug metabolism in women. For example plasma clearance of metoprolol increased 2–13 folds during pregnancy as compared to that after delivery [20]. Though drinking and smoking alter the activity of many CYPs, it is less significant in the case of 2D6 except regarding extensive metabolizers where it is slightly more. Alcoholic cirrhosis mainly affects the expression of drug transporters like SLCO but a minor impact on CYPs. Herbal medicines like Panax ginseng inhibits 2D6 activity by around 7% whereas goldenseal inhibits its activity by around 50% and thus has a potential for clinical interactions with drugs that are CYP substrates [21].

The human CYP2D6 enzyme is mainly uninducible by prototypical inducers like rifampicin, phenobarbital during in vitro studies whereas some in vivo studies have shown conflicting results. SHP (Small Heterodimer Partner), an orphan nuclear receptor can regulate the expression of CYP2D6 by inhibition. Another nuclear receptor HNF-4alpha (Hepatocyte Nuclear Factor) governs the transcription of CYP2D6, so that suppression of HNF 4 alpha causes decreases in mRNA levels of CYP2D6 [22]. Thus genetic variation in HNF can affect CYP levels. Liver specimens with heterozygous HNF-4alpha Gly60Asp genotype tend to have lower levels of CYP2D6 compared to wild type. NO (Nitric Oxide) through its effect on HNF-4alpha down regulate the transcription of 2D6. FXRs (Farnesoid X receptor) are nuclear hormone receptors which participate in bilirubin metabolism in liver, intestine, and kidney. FXR agonists like obeticholic acids decrease hepatic cyp2d6 expression suggesting the potential drug-drug interaction between CYP2D6 substrates and FXR agonists [22]. CYP2D6 is post-translationally modified by phosphorylation, but data regarding its regulation is limited. Genome-wide association studies (GWA) have shown that some SNPs like CYP2D6*4, *10 and *14 are associated with reduced activity of the enzyme. Of the 54 SNPs associated with CYP enzyme activities, 30 are related to CYP2D6 activity, and they are all located within 200 kb distance of the physical location of the CYP2D6 gene [23]. Diseases like liver disease, renal disease, rheumatoid arthritis and other inflammatory diseases have some effects on CYP activity. The liver disease reduces the activity of CYPs but has less effect on CYP2D6. Covalent binding of toxic metabolites to CYP leads to the formation of anti-CYP antibodies and immune-mediated hepatotoxicity. Liver Kidney Microsomal type1 antibodies (LKM-1) targeting CYP2D6 in hepatocytes are detected in the plasma of patients with chronic hepatitis C. Autoimmune hepatitis type B I characterized to be mainly related to drug-metabolizing enzymes as auto antigens, such as LKM-1 against CYP2D6.Antibodies might bring about a targeted functional inhibition via ligand like interaction at the level of the CYP2D6 cavity, corresponding to the dominant immune epitope. Further studies are needed to clarify the role of nuclear, epigenetic and other factors in the regulation of CYP2D6 as it seems to be less affected than other CYPs.

Table 1
List of drugs for which treatment guidelines are available.

CPIC Guidelines (Clinical Pharmacogenomics Implementation Consortium)	Amitriptyline, clomipramine, citalopram, codeine, desipramine, doxepin, escitalopram, fluvoxamine, imipramine, nortriptyline, paroxetine, sertraline, trimipramine
DPWG Guidelines (Dutch Pharmacogenetics Working Group)	Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline Propafenone, carvedilol, metoprolol, flecainide Clozapine, haloperidol, risperidone, zuclopenthixol, flupenthixol, aripiprazole Paroxetine, venlafaxine, duloxetine, mirtazapine, atomoxetine Codeine, oxycodone, tramadol Tamoxifen
CPNDS Guidelines (Canadian Pharmacogenomics Network for Drug Safety)	Codeine

Table 2
Functional classification of alleles of CYP2D6.

Null alleles	*3 *4 *5 *6 *7 *8 *11 *12 *13 *14 *15 *16 *18 *19 *20 *21 *38 *40 *42 *44 *56 *62 *68 *92 *10 *101
Alleles with partial function	*10 *14 *17 *18 *36 *41 *47 *49 *50 *51 *52 *54 *55 *57 *59 *69 *72
Alleles with largely normal or increased activity	*2A *17 × 2 *27 *35 *39 *41 × 2 *48

Table 3
List of approved drugs that includes CYP2D6 information in drug label.

US- FDA (US Food and Drug Administration)	Amitriptyline, arformoterol, aripiprazole, atomoxetine, brexpiprazole, carvedilol, cevimeline, citalopram, clomipramine clozapine, codeine, darifenacin, desipramine, doxepin, eliglustat, escitalopram, fesoterodine, flibanserin, fluoxetine, fluvoxamine, galantamine, iloperidone, imipramine, metoprolol, modafinil, nefazodone, nortriptyline, palonosetron, paroxetine, perphenazine, pimozide, propafenone, propranolol, protriptyline, quinidine, quinine, risperidone, terbinafine, tetrabenazine, thioridazine, timolol, tiotropium, tolterodine, tramadol, trimipramine, vortioxetine, dextromethorphan,quinidine,fluoxetine, olanzapine
EMA (European Medicines Agency)	Darifenacin, dronedarone, eliglustat, fesoterodine, gefitinib, olanzapine, propranolol, ranolazine, ritonavir, timolol, vortioxetine, dextromethorphan, quinidine, aripiprazole
HCSC (Health Canada Santé Canada)	Aripiprazole, atomoxetine, carvedilol, codeine, darifenacin, fesoterodine, galantamine, metoprolol, nortriptyline, propafenone, risperidone, tamoxifen, tetrabenazine, tolterodine, vortioxetine, acetaminophen, tramadol
PMDA (Pharmaceuticals and Medical Devices Agency)	Atomoxetine, tolterodine

8. Clinical pharmacogenomics of CYP2D6

In the 1970s and 80s, debrisoquine hydroxylation and exaggerated hypotensive effects from that drug were related to an autosomal recessive inherited deficiency in CYP2D6. Mahgoub et al. and Eichelbaum et al. have discovered that metabolism of debrisoquine and sparteine is polymorphic which was later shown to be due to CYP2D6 polymorphisms [24]. CYP2D6 can metabolize more than 160 drugs and cause significant effect on response and clearance of its substrate drugs. Several guidelines have come so as to maximise therapeutic effect and minimize toxicity. CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines are available for ten drugs, and DPWG (Dutch Pharmacogenetics Working Group) have put guidelines for 26 drugs see Table 1 [25].

Functionally alleles of CYP2D6 can be classified into three groups; alleles with normal or increased activity and decreased activity or loss of activity. See Table 2.

FDA (US Food and Drug Administration) has mentioned CYP2D6 effects in the drug labels of 48 drugs, EMA (European Medicine Agency) has listed it in13 drugs, HCSC (Health Canada sante Canada) in 16 drugs and PMDA (Pharmaceuticals and Medical Device Agency) in 2 drugs. See Table 3.

9. Conclusions and future perspectives

CYP2D6 polymorphism affects the clinical outcome of pharmacotherapy due to resulting metabolizer status. If the parent drug is active, then UMs may experience a lack of efficacy whereas PMs will suffer toxicity. A number of allelic variants have been added in the list which predicts the clinical success. Knowing more about the variants adds our knowledge and helps to develop treatment algorithms for many drugs. Given that genotyping test for CYP2D6 is not routinely performed in clinical practice, further prospective studies on the clinical impact of CYP2D6- dependent metabolism of drugs are warranted in large cohorts of samples.

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