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REVIEW PAPER

Cytochrome P450 2D6 and Parkinson's Disease: Polymorphism, Metabolic Role, Risk and Protection

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Abstract Cytochrome P450 (CYP) 2D6 is one of the most highly active, oxidative and polymorphic enzymes known to metabolize Parkinsonian toxins and clinically established anti-Parkinson's disease (PD) drugs. Albeit CYP2D6 gene is not present in rodents, its orthologs perform almost the similar function with imprecise substrate and inhibitor specificity. CYP2D6 expression and catalytic activity are found to be regulated at every stage of the central dogma except replication as well as at the epigenetic level. CYP2D6 gene codes for a set of alternate splice variants that give rise to a range of enzymes possessing variable catalytic activity. Case-control studies, meta-analysis and systemic reviews covering CYP2D6 polymorphism and PD risk have demonstrated that poor metabolizer phenotype possesses a considerable genetic susceptibility. Besides, ultra-rapid metabolizer offers protection against the risk in some populations while lack of positive or inverse association is also reported in other inhabitants. CYP2D6 polymorphisms resulting into deviant protein products with differing catalytic activity could lead to inter-individual variations, which could be explained to certain extent on the basis of sample size, life style factors, food habits, ethnicity and tools used for statistical analysis across various studies. Current article describes the role played by polymorphic CYP2D6 in the metabolism of anti-PD drugs/Parkinsonian toxins and how polymorphisms determine PD risk or protection. Moreover, CYP2D6 orthologs and their roles in rodent models of Parkinsonism have also been mentioned. Finally, a perspective on inconsistency in the findings and futuristic relevance of CYP2D6 polymorphisms in disease diagnosis and treatment has also been highlighted.

Keywords Parkinson's disease · Cytochrome P450 2D6 polymorphism · Risk · Protection

Introduction

Parkinson's disease (PD) is one of the most unexplained, chronic, progressive and prevalent movement disorders, differentiated by the selective demise of tyrosine hydroxylase positive or dopamine producing neurons in the nigrostriatal pathway of the central nervous system [1–4]. Although tuberoinfundibular, mesolimbic and mesocortical dopaminergic pathways of the central nervous system are also enriched with monoamine producing neurons, mainly dopaminergic neurons of the nigrostriatal pathways are found to be susceptible in PD [1–5]. Loss of dopamine producing cells in the substantia nigra goes on and aggravates over time leading to the striatal dopamine deficiency and decline in the number of dopaminergic fibers [6]. Consistent and prolonged depletion of dopamine result in the motor impairment that include tremor at rest, stiffness in the muscles, difficulty in changing the posture and slowness in performing the emotional, voluntary and indented movements [2, 4, 7]. As disease progresses, patients develop secondary symptoms, such as freezing, asymmetrical hand writing, difficulty in drooling of saliva, etc. PD pathologically makes a distinction owing to the presence of intracytoplasmic protein aggregates, commonly referred to as Lewy bodies, in the

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surviving dopaminergic neurons [3]. Although increasing age has been the foremost culprit, genetic predisposition and exposure to environmental toxicants, such as agrochemicals, have also been shown to contribute to PD pathogenesis [2, 3, 8].

Cytochrome P450 2D6 enzyme (CYP2D6), encoded by the gene CYP2D6, is a mixed-function oxidase. CYP2D6 gene is located adjacent to two pseudogenes on the q13.1 arm of the chromosome 22 [9, 10]. This enzyme is contained mostly in the human liver microsomes. Albeit abundantly present in the liver, expression of CYP2D6 isoforms in the substantia nigra and neighboring brain regions has also been reported [11, 12]. CYP2D6 enzyme is responsible for the metabolic activation/deactivation/oxidation/dealkylation of a number of commonly used and clinically proven drugs along with a few neurotoxins. Expression and catalytic activity of CYP2D6 is controlled by a variety of modulators [12–16]. CYP2D6 isoforms distinctly contend and competitively inhibit the metabolism of other substrate, if available at the same time [12–16]. Owing to alternate splicing of the gene, CYP2D6 enzyme is found to be highly polymorphic in nature and several functionally active isoforms and more than 70 distinct splice variants have been identified [15].

Absence of functionally active CYP2D6 gene and lack of naturally occurring PD in rodents prompted investigators to look into the role of CYP2D6 orthologs in toxin-induced Parkinsonism in experimental rodents. A few CYP2D6 orthologs, such as mouse cyp2d22 and rat Cyp2d2/Cyp2, etc., have been identified and their role in PD has been proposed [17–19]. Inconsistent phenotypic features, absence of naturally occurring PD in rodents and incoherent effect of a neurotoxin in animals and humans could be partially explained owing to the presence of various forms/orthologs of human CYP2D6. CYP2D6 is highly polymorphic and is unrelated to some extent with animal orthologs in terms of catalytic activity, substrate specificity and response towards inhibitors in spite of having the significant functional and structural homologies. Debrisoquine is a known specific substrate and 4-hydroxydebrisoquine is a major intermediary metabolite of human CYP2D6. Regardless of these, more than 100 strong, weak or intermediate inhibitors and substrates along with a small number of inducers have been recognized. Responsiveness and specificity of CYP2D6 or its orthologs towards a substrate, inhibitor or agonist vary owing to differences in their structure and endogenous and exogenous environmental predispositions [13–15]. Moreover, the substrate and inhibitor responsiveness of mouse cyp2d22, a human CYP2D6 ortholog, is analogous to human CYP3A4 [17].

Inter-individual variation in drug clearance, effectiveness and toxicity is contributed by CYP2D6 and its orthologs at least in one-fourth of the clinically proven drugs [14]. CYP2D6 expression or catalytic activity is individual-specific, particularly when a functional single nucleotide polymorphism (SNP) is present in the coding or regulatory region of the gene. CYP2D6 gene codes for several splice variants that are translated to highly inconsistent proteins in terms of function. A variant could express highly efficient or least handy form of protein or between the two. Based on the catalytic activity of the resultant protein products, CYP2D6 carriers have been classified into four major categories. Poor metabolizers, if the catalytic function of the enzyme is too low or completely lost, extensive or normal metabolizers when the enzyme performs entirely normal function, intermediate metabolizers, if CYP2D6 activity is seen between the first two and ultra-rapid metabolizers when the enzyme activity is more than the normal due to the presence of multiple copies of CYP2D6 gene [20–23]. Type of metabolizers not only determines disease risk but also conclude the efficacy, toxicity or effectiveness of a chemical since many Parkinsonian toxins and anti-PD drugs are found to be metabolized by CYP2D6 enzyme. Percentage of poor metabolizers is found to be relatively more in the whites while ultra-rapid metabolizers are found to be relatively high in the Middle East and North Africans showing the likely cause of variable disease risk between the two populations and risk inconsistency between the two individuals exposed to the same environment [21–23]. Despite lower CYP2D6 content in the frontal cortex, cerebellum and hippocampus, similar level in the substantia nigra and striatum is observed in PD patients in a study [16]. However, lower CYP2D6 level could reduce its ability to inactivate Parkinsonian toxins that contribute to disease risk [16].

Function and Structure of CYP2D6

After CYP3A4, CYP2D6 metabolizes the maximum number of endogenous and exogenous chemicals generally used to encounter neurological disorders along with neurotoxins and steroids. CYP2D6 or its orthologs convert such substances into electrophilic intermediates in the brain. CYP2D6 and its orthologs are known to chemically modify, i.e., hydroxylate, demethylate or alkylate the specific group of many drugs/Parkinsonian toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and paraquat [13–16, 18]. Electrophilic intermediates are further changed to hydrophilic derivatives by the phase II xenobiotic metabolizing enzymes and eliminated out of the body. A total of around one-fourth of the clinically used drugs is catabolized by the incorporation or omission of any of the above-mentioned functional groups. Besides, CYP2D6 is also involved in the metabolism of tryptamines, steroids and tyramines in the central nervous system. CYP2D6 also synthesizes dopamine from the endogenous and exogenous tyramine [13, 14]. Catalytic activity of CYP2D6 is highly dependent on its interaction

with other drugs acting as inhibitors or substrates. MPTP, a Parkinsonian toxin, gets activated to 1-methyl-4-phenyl-2, 3-dihydropyridinium ion ($MPDP^+$) and 1-methyl-4-phenylpyridinium ion (MPP^+) ions while deactivated to MPTP N-oxide or 4-phenyl-1,2,3,6-tetrahydropyridine (PTP). CYP2D6 is reported to participate in the activation of MPTP to $MPDP^+$ and MPP^+ [24]. Similarly, CYP2D6 orthologs, such as cyp2d22 is reported to participate in the metabolism of paraquat and MPTP in experimental mice [17, 18]. Owing to virtual contribution of CYP2D6 and its orthologs in the metabolism of Parkinsonian toxins and anti-PD drugs, they are implicated in controlling the risk to sporadic and toxins-induced PD. CYP2D6 could modify drug efficacy and bioavailability and could be helpful in developing personalized therapy based on the genotype of PD patients. Since CYP2D6 synthesizes dopamine and metabolize MPTP, paraquat, 1,2,3,4-tetrahydroisoquinoline, etc. and purges several other Parkinsonian toxins, its over-expression with normal or enhanced catalytic activity could be associated with neuroprotection [12, 14]. Contrary to the cytosolic form, the mitochondrial CYP2D6 in dopaminergic neurons is capable of activating MPTP and therefore inducing the neuronal damage that can be prevented by its inhibitors [25]. Besides, CYP2D6 ortholog modulates MPTP activity and protects from the nigrostriatal dopaminergic neurodegeneration in mice [17].

CYP2D6 gene is highly polymorphic, contains 9 exons and 8 introns and spans 4378 bp in the length [26] (Fig. 1). So far, roughly 80 polymorphic alleles have been identified in CYP2D6 gene and 5 are found to be commonly associated with PD [27] (Fig. 1). CYP2D6-mediated metabolism of drugs and chemicals is achieved through the activation of oxygen by the heme group. Attack of two electrons breaks dioxygen bond leading to water and activates iron-oxygen biosynthesis, which reacts with CYP2D6 substrates. The crystal structure refined to 3.0 Å resolution have shown P450 fold with the length and orientation of specific secondary structure involving F helix, F-G loop, β-helix, β-sheet 4 and part of β-sheet 1 located on the distal face [28]. Active site cavity above heme group is found to contain Asp-301, Glu-216 and Phe-483 as substrate binding residues and Phe-120 as an orientation regulator of the aromatic ring of the substrate [28]. Typical CYP2D6 substrates are lipophilic bases with an aromatic ring and a nitrogen atom that can be protonated at the physiological pH. Substrate binding is usually followed by oxidation from nitrogen-Asp-301 interaction [29].

CYP2D6 Polymorphism and PD Risk

SNP occasionally results in the gain or loss of CYP2D6 function and often does not alter the expression or catalytic activity. However, SNP located in the region, which regulates transcription or mRNA stability or leads to an alteration in the nature or sequence of the amino acid, could alter the function of the resultant protein. CYP2D6 SNPs resulting in poor metabolizers, intermediate metabolizers, extensive metabolizers and ultra extensive metabolizers have been identified. Such SNPs lead to the generation of a number

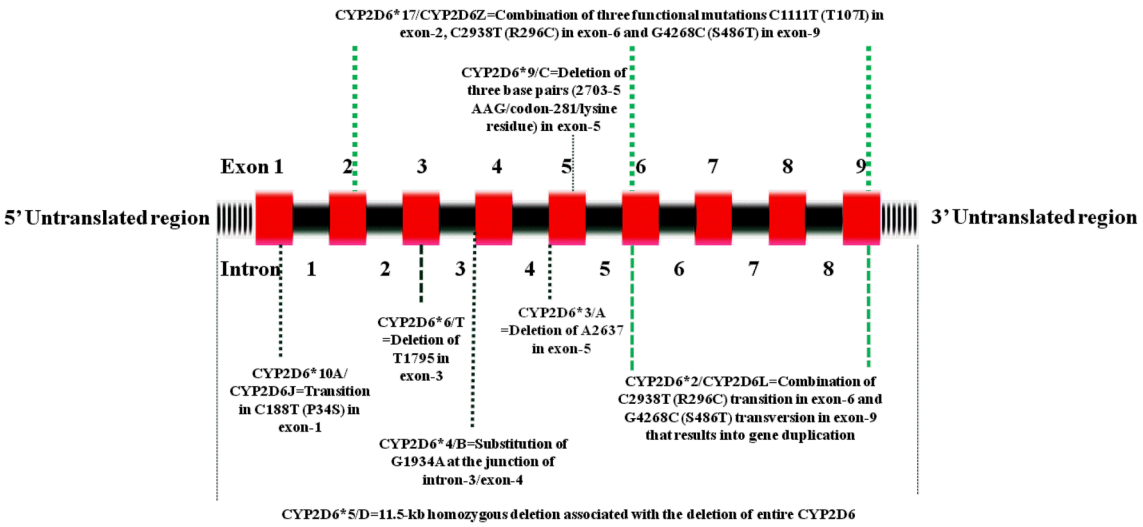

Fig. 1 Literature based schematic presentation of CYP2D6 and summary of the major variants associated with PD risk. CYP2D6A and CYP2D6T variants result from the point mutations leading to emergence of premature stop codons. While CYP2DB leads to premature termination, CYP2D6D leads to deletion of entire gene/11.5Kb Xba I fragment. CYP2D6C, CYP2D6J and CYP2D6Z variants are associated with reduced and CYP2D6L variant is associated with increased catalytic activity. CYP2D6 is basically composed of 9 exons, 8 introns and spans 4378 bp

of genetic variants, which direct variable PD risk owing to inconsistent substrate and toxin metabolism [28–44]. Type of variants and their effect on PD risk and debrisoquine metabolism are summarized in Table 1. Significant association of CYP2D6 polymorphism with PD is demonstrated in the British whites but not in other white subjects as well as not with the age of onset [45]. In such subjects, poor metabolizer phenotype of CYP2D6 confers a significant genetic susceptibility towards PD [45]. Genetically poor CYP2D6 metabolizers are found to be at higher risk for developing PD that increases with exposure to pesticides [16].

A few polymorphisms that include CYP2D6*4, CYP2D6*3 or CYP2D6*5 (Fig. 1) are found to occur in unequal frequencies and reported to have link with PD risk in one or the other population [15]. CYP2D6*4 G-to-A transition polymorphism located at the junction of intron-3 and exon-4 leads to an introduction of a nonsense codon, which gives birth to a protein that lacks substantial catalytic activity [32, 36] (Fig. 1). Polymorphism in intron-3 at 3-prime splice site (CYP2D6*4) is a general source of poor metabolizer phenotype [46]. An association between CYP2D6*4 allele underlying a poor metabolizer phenotype and age of PD onset suggests a protective advantage of variant allele over the wild type [46]. Moreover, a meta-analysis relating to CYP2D6*4 polymorphism and PD risk has demonstrated its association with the Caucasians but not with the Asians. On the other hand, no significant association is found in subgroup analysis stratified by the age of onset or form of disease [32]. Individuals who are homozygous for CYP2D6*4 allele and had pesticide exposure are found to be at high PD risk [47]. CYP2D6*3 2637A deletion in exon-5 results in a truncated protein with negligible catalytic activity [30]. Negligible catalytic activity could be associated with an altered PD risk. CYP2D6*AA genotype is also an important risk determinant for an early onset of disease [48]. CYP2D6*4, CYP2D6*3 or CYP2D6*5 homozygous allele

Table 1 A list of CYP2D6 variants associated with PD risk: name of variants, associated risk and effect on debrisoquine metabolism are mentioned in the table based on the information available in the literature. Exposure to pesticides is found to increase the risk in a few studies [30–44]

Sl. no.	CYP2D6 variant and major structural change	PD risk	Effect of environmental factors on risk	Substrate metabolism/enzyme activity
1	CYP2D6A/CYP2D6*3 is characterized with A2637 deletion in exon-5	Increased	Increased, more in homozygous variant	Poor/absent activity
2	CYP2D6B/CYP2D6*4 is featured with G1934A substitution at the junction of intron-3/exon-4	Increased	Increased, mainly in homozygous variant	Poor/absent activity
3	CYP2D6C/CYP2D6*9 variant contains 3 base pairs deletion in exon-5 and results in codon 281/lysine residue deletion	Increased	Not yet clear	Intermediate /reduced activity
4	CYP2D6D/CYP2D*5 is a variant characterized with 11.5-kb homozygous deletion or deletion of the entire gene	Increased	Increased, more in homozygous variant	Poor/no activity
5	CYP2D6T/CYP2D6*6 is associated with T1795 deletion in exon-3 leading to pre-mature termination	Increased	Increased mainly in homozygous variant	Poor/absent activity
6	CYP2D6J/CYP2D6*10A is characterized with transition at C188T (P34S) in exon-1	Increased	Not yet known	Poor/reduced activity
7	CYP2D6L/CYP2D6*2 variant is a combination of C2938T (R296C) transition in exon-6 and G4268C (S486T) transversion in exon-9 resulting into gene duplication	Reduced in homozygous/unaltered in heterozygous	Not yet known	Ultra-rapid/increased activity
8	CYP2D6Z/CYP2D6*17 variant is a combination of three functional mutations, i.e., C1111T (T107I) in exon-2, C2938T (R296C) in exon-6 and G4268C (S486T) in exon-9	Not yet clear	Not yet known	Intermediate/reduced activity

is seen to be associated with an increased risk of PD, if pesticide exposure is also present [49]. However, no significant association is found between CYP2D6 genotype and PD risk in a different study [50]. Moreover, extensive metabolizers are found to be at higher risk than the corresponding poor/intermediary metabolizers [50]. While many epidemiological studies have explored an association of a CYP2D6 SNP with PD risk, assessment of association of multiple SNP with PD risk is still limited [32].

CYP2D6, Nicotine and Smoking

CYP2D6 metabolizes little less than 200 drugs and causes a huge inter-individual variability in the clearance, response and interaction of a drug with other drugs [20]. It is regulated by the type and specificity of the substrate, inhibitor, endogenous and exogenous environmental factors and drug–drug interaction at the mRNA, protein and epigenetic levels [20]. Smoking and nicotine consumption have been widely associated with reduced PD risk. Even though, CYP2D6 is not directly involved in the metabolism of nicotine per se or nicotine in smokers [51]. Rather, studies have shown its role in nicotine-mediated neuroprotection owing to its influence on nicotine disposition. Role of genetic predisposition and occupational risk factors in Italy, Malta, Romania, Scotland and Sweden was assessed to explore the contribution of such interactions with PD risk [52]. Albeit CYP2D6 is not an inducible enzyme in the liver, it is induced by a number of agents in the substantia nigra, striatum and adjacent regions in the basal ganglion of the central nervous system. High CYP2D6 activity (bufuralol 1′-hydroxylation) is found in the substantia nigra showing the likelihood of CYP2D6-mediated dopamine synthesis as a decisive factor in PD pathogenesis and addiction process [14, 53]. Induction is seen in the substantia nigra and striatum of smokers or even after chronic nicotine exposure [54]. Smokers or nicotine exposed animals have higher level of CYP2D6 or its ortholog protein resulting into an altered drug metabolism and inactivation of neurotoxins [54, 55]. Post-translational modification, such as Ser-135 phosphorylation in CYP2D6, is found to regulate the response but functional validation is still needed to shed the light on the role of nuclear receptors, epigenetic factors and endogenous and exogenous modifiers in its regulation [20].

Despite smoking has negative association with PD, altered catalytic activity or expression owing to CYP2D6 polymorphism is not observed in a case-control study [52]. However, increased frequency of CYP2D6*2, CYP2D6*4 and CYP2D6*10A (188C/T) polymorphisms in PD is seen and a combination of heterozygous genotypes (CYP2D6*4, CYP2D6*10A/188C > T and NAT2*5) is found to be at higher risk that signify the role of genetic interactions [39, 52]. In another study, which is conducted on the subjects of Faroe Island, CYP2D6 is not distinctly found to be associated with PD. However, high frequency is found to be the result of an interaction between the genes and environment [55]. Roles of CYP2D6 genotype and allele distribution, CYP2D6 allele and age of onset/advancement of dementia and CYP2D6 allele and dose/side effect of levodopa in sporadic PD with dementia could not be established with conviction leading to an uncertainty, if CYP2D6 is a key contributor to PD risk or not [56].

Environmental Toxicants, PD and CYP2D6

Alterations in CYP2D-mediated metabolism by endogenous chemicals could modify the sensitivity to environmental toxicants [13]. A poor metabolizer is always at a high risk for developing PD especially if exposed to high level of environmental toxicants, such as agricultural pesticides, insecticides and herbicides [57]. A few environmental and non-environmental toxicants (incorrectly but popularly referred to as toxins) are used to develop animal models that mimic some of the cardinal features of PD [7]. Toxicant models are usually classified into traditional/conventional and combinational models. Conventional models employ either well-known chemical entities, such as 6-hydroxydopamine (6-OHDA), rotenone and MPTP or newly recognized Parkinsonian toxicants, such as paraquat (an herbicide), cypermethrin (an insecticide), maneb (a fungicide) and iron (a heavy metal) to induce disease symptoms. Moreover, several organochlorine, carbamate, organophosphate and pyrethroid pesticides and heavy metals have also been shown to bring forth PD like features, including striatal dopamine depletion and nigrostriatal dopaminergic neurodegeneration [2, 4, 6, 7]. Organochlorine pesticides are found to be present in higher concentration in the substantia nigra and striatum enlightening the existence of a possible association among organochlorine pesticides, PD and CYP2D6 polymorphism [58, 59]. On the other hand, even ambient exposure to organophosphate pesticides has been shown to be associated with PD [60]. While a link between organochorine pesticides and PD is extensively studied, contribution of pyrethroids and organophosphates has limited but highly supportive epidemiological and animal data showing their association with PD [60–62]. Pyrethroids are not directly metabolized by this enzyme but organophosphate and carbamate pesticides are found to be metabolically activated by CYP2D6 suggesting that polymorphism in this gene could categorically influence the overall toxicity of such environmental toxicants [63, 64].

Owing to variable chemical nature, route and site of administration and tissue specificity, environmental toxicants induce variable Parkinsonian features. A few toxicants directly cross the blood brain barrier owing to lipophilic

nature, such as rotenone and MPTP while others exploit specific transporter, such as paraquat or passive transport, such as maneb [4, 7]. 6-OHDA and MPTP provide clues to the basic understanding of disease pathogenesis and assessment of therapeutic efficacy. 6-OHDA and MPTP also reduce the striatal dopamine content and degenerate the nigral dopamine producing neurons but do not elicit the progressive demise of neurons and distinct Lewy body formation [6, 7]. Contrary to them, paraquat (a bipyridine), organophosphates and cypermethrin (a pyrethroid) are known to induce the nigral dopaminergic neuronal loss and striatal dopamine depletion in a progressive manner. At high doses and long-term exposures, paraquat produces severe toxic response. While organophosphates and pyrethroids are not yet extensively studied, these are specific in nature [61, 62]. Moreover, rotenone, an isoflavone pesticide, induces nigrostriatal dopaminergic neurodegeneration and Lewy body formation and maneb, a fungicide, induces PD phenotype in combination with some other toxicant, such as paraquat [2, 7, 8]. While rotenone exhibits some resemblance with sporadic PD, it is highly non-specific in nature. Carbamates (such as maneb) are not found to be as effective as other toxicants. All known Parkinsonian toxicants are shown to inhibit the mitochondrial complex I except maneb and dieldrin (an organochlorine) that inhibit complex III [2, 4, 6, 7]. Combinational models are developed either by the combination of two toxicants, such as MPTP and cypermethrin and maneb and paraquat or by an amalgamation of a toxicant and a mutation induced in a PARK gene, such as MPTP and α-synuclein over-expression system [7]. Such models possess additional benefits and restraints over the classical models. Epidemiological evidences have shown an active role of CYP2D6 since fewer incidences of PD are seen in the populations exposed to environmental toxicants if individuals carry high metabolizer genotype. An altered CYP2D6 activity could be responsible for modulation in bio-activation of environmental chemicals thereby altered PD incidences [47, 49, 57]. Exposure to environmental toxicants, such as pesticides, increases the risk of PD up to two folds in the poor metabolizers (CYP2D6*4) as compared with normal metabolizers in a population [47]. Poor metabolizer status is also correlated with an increased PD risk in the populations exposed to environmental toxicants, such as agrochemicals [57]. Moreover, poor metabolizers (CYP2D6*3, CYP2D6*4 and CYP2D6*5) exposed to environmental toxicants are found to be at higher risk of developing PD in another population [49].

CYP2D6 Orthologs and Parkinsonism

Parkinsonism in animals is also regulated by the age, genetics and environmental exposure to neurochemicals and toxins [17, 62]. It is therefore speculated that like human CYP2D6, other CYP2D6 orthologs could play a role in the metabolism of various neurotoxins and anti-PD drugs. In rats, a total of six CYP2D isoforms have been successfully identified [65]. However, it is not yet clear which one is the genuine human CYP2D6 ortholog. Also, unlike human CYP2D6, substrate or inhibitor response is found to be unique and highly tissue specific [65]. Similarly, CYP2D7 is found to metabolize codeine to morphine unlike hepatic CYP2D6 that metabolizes codeine to nor-codeine and morphine [66]. A frame-shift mutation (138delT), in the subjects who express variant CYP2D7, is observed in a study indicating an existence of an alternate functional splice variant containing partial inclusion of intron-6 in the brain but not in the liver or kidney [66]. Bufuralol 1′2′-ethenylation activity is highly specific to CYP2D4 while debrisoquine 4-hydroxylation and propranolol 7-hydroxylation are shown to be specific to CYP2D2 [65]. Rat isoforms of CYP2D6 are also found to regulate nicotine metabolism and associated with neuroprotection. Nicotine exposure activates or inactivates endogenous chemicals due to an increased level of CYP2D in the rat brain [19]. Chronic nicotine exposure gradually induces CYP2D in the rat brain up to 8 h and the process is regulated at the posttranscriptional level similar to human CYP2D6 [19, 20]. However, the level of rat liver CYP2D enzymes is found to be unchanged after nicotine exposure [19].

In a transgenic mouse model, various forms of CYP2D protein are found to be detectable in the brain, showing a correlation among rodents and human [67]. The cyp2d22, a mouse ortholog of human CYP2D6, is found to play a key role in chemically-induced Parkinsonism [17]. It is found to improve nicotine-mediated protection thus showing its likely contribution in PD pathogenesis [17, 18]. MPTP level is regulated by the expression/catalytic activity of cyp2d22 while ketoconazole is found to reduce the nicotine-mediated changes. Likewise, cyp2d22 is found to offer protection against pesticides-induced PD, regulates paraquat metabolism and enhances neuroprotective credential of resveratrol [18].

Basis of Inconsistent Results, Relevance of CYP2D6 Polymorphism and Future Directions

Undeniably, CYP2D6 polymorphism plays a decisive role in the metabolic regulation of many drugs and neurotoxins. Hypothetically, it can regulate disease risk as well as protection even in the same individual particularly when a person is naturally/unintentionally exposed to a Parkinsonian toxin and an anti-PD drug if both are metabolized by CYP2D6. For example, MPTP is metabolized by CYP2D6 so is true for some anti-PD drugs. Therefore, it is idyllically difficult

to predict risk/protection in the normal or extensive metabolizers if carrier individuals are exposed to them. Besides hypothetical points, association of CYP2D6 with PD risk/protection is widely established. Despite all, a conclusive correlation could not be drawn yet and contradiction among studies has been noticed. As a result, defining the relationship between PD and CYP2D6 has been a matter of intense debate from the last two decades but convincing explanation is still awaited. Several studies have found a link while others have failed to get any relationship. Varying ethnicity, food habit and life style factors could be possible explanations since structure of CYP2D6 shows an interethnic variation and its activity is exaggerated by such variables [47, 68]. "Does polymorphic CYP2D6 dependably determine PD risk?" catchphrase is challenging and needs agreeable reply from the scientific fraternity.

Genetic variability in drug responsiveness is theoretically approved and is widely accepted. Concept of the development of personalized therapy is also proposed around two decades ago. However, personalized therapy depending on CYP2D6 genotype of a patient has been rarely recommended in the clinics even in the developed countries with the best of our knowledge. Four major justifications could possibly explain the issue. First, the same aspect is theoretically correct for the risk if Parkinsonian toxins are also metabolized by CYP2D6. Genotype and rate of drug metabolism and its interaction with another drug have not yet been precisely studied, mainly when chronic administration is given to the patient. Second, genotype-phenotype association could not be ascertained from the studies performed in various ethnic groups or even in two studies of the same ethnic group [32, 45]. Inconsistent experimental paradigms, confounding factors, research methodologies, data analysis tools, biostatistics, individual research ethics and sample size employed in various studies could also be the likely culprits. Third, lack of wide variety of drugs to treat chronic diseases also limits the selection of a personalized medicine to treat the patient. Moreover, variation in the metabolism could lead to toxicity or remedial failure since drug efficacy depends on the dose and concentration of its metabolite in the blood [68]. Occasionally, drugs metabolized by CYP2D6 in the brain could accumulate and produce disease symptoms instead of treatment [68]. Medical decisions in clinical practice and intervention to tailor an individual patient-based medicine for improved efficacy and minimal toxicity are still hypothetical, except in a fewer classic cases. Certainly, the selection of an effective drug in appropriate dose without toxicity based on CYP2D6 genotype has not yet been achieved in PD patients. While a personalized drug is expected to encounter PD more effectively in the coming years, the studies give an impression that the field is still in the fascinating ring of theoretical medical science. More time is needed to indemnify the regulatory, confidentiality and personalized rights of PD patients and to defeat the current difficulties. Only after accessibility of supplementary, all-embracing and highly specific newer association studies and innovative triumph in drug development program along with the creation of comprehensive toxicity data for the existing drugs, CYP2D6 genotype-based therapy could be considered for approval in clinics.

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Compliance with Ethical Standards

Conflict of interest Authors state that they do not have any conflict of interest.

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