Pharmacogenomics of CYP2D6: Molecular Genetics, Interethnic Differences and Clinical Importance

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Summary: CYP2D6 has received intense attention since the beginning of the pharmacogenetic era in the 1970s. This is because of its involvement in the metabolism of more than 25% of the marketed drugs, the large geographical and inter-ethnic differences in the genetic polymorphism and possible drug-induced toxicity. Many interesting reviews have been published on CYP2D6 and this review aims to reinstate the importance of the genetic polymorphism of CYP2D6 in different populations as well as some clinical implications and important drug interactions.

Keywords: CYP2D6 polymorphism; interethnic differences; clinical implication

CYP2D6 Genetic Polymorphism

Cytochrome P450 (CYP) 2D6 is one of the most widely investigated CYPs in relation to genetic polymorphism. Typical substrates for CYP2D6 are largely lipophilic in nature and include antidepressants, antipsychotics, antiarrhythmics, antiemetics, beta-adrenoceptor antagonists (beta-blockers) and opioids, which represent approximately 25% of currently marketed drugs.1–3 The enzyme is largely non-inducible and represents 1–5% of the total P450 in the liver.4–6 One of the reasons for the large research interest of this enzyme is the wide inter-individual variation in the enzyme activity of CYP2D which led to discovery of deletion and duplication of the CYP2D6 gene. In addition, the discovery of CYP2D6 polymorphism7–9 has created new interest in the role of pharmacogenetics in clinical pharmacology since the 1970s.

Molecular Genetics of CYP2D6

CYP2D6 is the only functional gene in the CYP2D subfamily of the human genome.10 To date, more than 80 allelic variants have been reported for CYP2D6 (http://www.imm.ki.se/cypalleles/cyp2d6.htm). The most common functional polymorphism in drug metabolizing enzymes (DMEs) is point mutations in coding regions of the CYP2D6 gene resulting in amino acid substitutions, which alter catalytic activity, enzyme stability, and/or substrate specificity.

The CYP2D6 gene is localized on chromosome 22q13.1. It contains 9 exons11 within 4,383 bp based on the NCBI 37 genome assembly. The evolution of the human CYP2D locus has involved elimination of three genes and inactivation of two neighbouring genes (CYP2D7 and CYP2D8P) and partial inactivation of one CYP2D6. These genes display 92–97% nucleotide similarity across their introns and exons. The CYP2D8P gene was found to be a pseudogene and to contain several gene-disrupting insertions, deletions, and termination codons within its exons. CYP2D7, which is just downstream of CYP2D8P, is apparently normal, except for the presence, in the first exon, of an insertion that disrupts the reading frame. These two closely related genes were believed to transfer detrimental mutations via gene conversions into the CYP2D6 gene and were hypothesised to account for the high prevalence of variants which most commonly encode defective gene products.

A combination of polymorphisms, including SNPs, duplications, insertion/deletions and/or gene conversions, have been reported to cause increased or reduced CYP2D6 enzyme activity. These alleles include 7 normal or increased activity alleles [*1,11,12 *2,12–17 *27,12,15 *33,12 *35,12,18,19 *48,15,20 *5315,21], 11 alleles with reduced activity [*9,22]
There are pronounced differences in the prevalence of PMs and in the relative enzyme activity in different ethnic groups. The overall prevalence of PMs was 7 to 10% in Caucasian populations and was rare in other populations. In Asians, PMs occurred at 0–1% due to the low frequencies in Asia of CYP2D6*3 and *4, which were the most abundant null alleles in Caucasians, and CYP2D6*2, *3, *4, *5, *6, *10, and *41 being more common in the Caucasian population, *2 and *17 more frequently observed in Africans and CYP2D6*10 and *36 more prevalent in Asians. It is interesting to note that the frequency of PMs remained relatively constant among Caucasians in different continents. Similarly, the Chinese, Thai, Singaporeans, Japanese, and Malaysian Malays also showed lower prevalence. However, despite their localization the New Zealand Maori had a frequency of PMs similar to that of Caucasians.

CYP2D6*10 is the most common allele in Asians. The CYP2D6*10 enzyme has a P34S substitution resulting in an unstable enzyme with reduced affinity for CYP2D6 substrates. CYP2D6*10 has the hallmark nucleotide change of C to T at 100, which is also present in CYP2D6.17 enzyme shows an altered active site structure due to the two missense alleles and its frequency was 34% in Zimbabweans. The activity of CYP2D6 was lower among Africans and showed lower prevalence. However, their localization the New Zealand Maori had a frequency of PMs similar to that of Caucasians.

Another allele which was found commonly among Africans is CYP2D6*17. Among the Blacks, Masimirembwa et al. found a right shift of metabolic ratio MR and showed the presence of CYP2D6*17 and its frequency was 34% in Zimbabweans. The activity of the CYP2D6*17 enzyme is lower than that of the wild-type enzyme and the CYP2D6*17 enzyme showed an altered active site structure due to the two missense mutations seen in CYP2D6*2 and T107I. Different enzymatic effects have been shown with different substrates such as codeine, debrisoquine, dextromethorphan and metopolol.

In contrast to the consistency of percentage of PMs, the percentage of duplicated/multiduplicated genes varies in different populations. In Swedish Caucasians, the frequency of subjects having duplicated/multiduplicated genes is about 1–2%. The frequency increases to 7–10% in Spain and becomes as high as 29% in black Ethiopians. Studies in Asian countries, revealed 1 to 2% of the Japanese, Chinese, Malays and Indians have gene duplication. In Figure 1, the distribution of the debrisoquine/4-hydroxydebrisoquine MR is bimodal in a large Swedish Caucasian population. PM have an MR higher than 12.6 and are homozygous for mutated alleles, to a major extent CYP2D6*4. UMs with low MR have multiple functional alleles. In one Swedish family, 13 active CYP2D6 genes have been demonstrated.
CYP2D6*36 is absent in white populations, but present in Asian and African American populations. CYP2D6*36 may have originated in Africa and spread to Asia but not Europe. CYP2D6*36 is accountable for the PM status in Asians and African Americans (3% and 0.5% respectively). Generally, the type and allele frequencies of CYP2D6 among Caucasians are different from those in Asians and Africans. Interestingly, Indians have similar types and frequencies of CYP2D6 alleles with Caucasians. They have lower frequencies of CYP2D6*10 and higher frequencies of *4 compared to the Japanese, Chinese and Malays. In fact, Indians are the eastern most settlement of the Caucasian “race” and thus classified as Caucasians.

Clinical Significance of Treatment with CYP2D6 Substrates

The clinical significance of the genetic polymorphism of CYP2D6 will be reviewed with respect to its importance to pharmacokinetic variation and disease association. A number of factors govern the clinical importance of the polymorphism, which include the nature of the primary metabolism pathway and mechanism that activate the parent compound, the potency of the parent compound and its metabolite(s), and the therapeutic windows of the drugs. A drug with an easily saturable metabolism tends to have a narrow therapeutic index, and the contribution of several pathways of elimination needs to be considered in the prediction of its effect. As one substrate may be metabolised by several different enzymes, the clinical impact of CYP2D6 dependent-metabolism needs to be carefully investigated for each substrate. This has been illustrated in a clinical context of accidental toxicity, whereby the precise dose of nortriptyline was determined by the combined effect of both CYP3A4 and CYP2D6.

Another major impact of a genetic polymorphism for first-pass extraction can be expected for drugs with a high hepatic clearance. EMs may have low bioavailability of drugs with a high hepatic (and possibly intestinal) extraction while the extraction may be impaired in PMs and result in increased bioavailability. On the other hand, drugs with a low hepatic clearance can have a high bioavailability in EMs, which will be similar in PMs. However, the interphenotypic differences exist mainly if these drugs are administered orally.

Genetic polymorphisms of CYP2D6 result in 4 phenotypes with significant clinical implication especially the PM and UM. PMs exhibit decreased metabolism of drugs and thus require lower dosages to avoid toxic effects. Adverse effects due to elevated drug plasma levels occur more frequently in PMs in cases where the drug clearance is dependent on CYP2D6. On the other hand, PMs can experience diminished effects with drugs that need to be metabolised to active compounds by CYP2D6. A popular example is codeine, which is a prodrug and needs to be converted to morphine in patients. Inadequate transformation in PMs leads to diminished pain relief or even tolerance/addiction. On the other extreme is the UMs who have more than two functional alleles due to gene duplication or multiplication. UMs would require lower doses of codeine than normal, since transformation of codeine to morphine is enhanced. UM patients given drugs active per se may be resistant to such treatment, and more time may be required to adjust the dosage before therapeutic efficacy is achieved. In theory, identifying a CYP2D6 UM...
up-front, would decrease the time needed to adjust a dosage upward, helping to achieve therapeutic success faster (Fig. 2). Recently, Black et al.,\(^{107}\) revisited the issue of CYP2D7-2D6 hybrid genes in samples with duplication signals and predicted UMs. Of 341 samples with duplication signals, 25 (7.3%) harbored an undetected CYP2D7-2D6 hybrid and had a change in predicted phenotype. Over-estimation of UMs among clinical samples would result in higher doses recommended to patients and carries risks of toxicity.

**Genetic polymorphism of CYP2D6 and psychotropic drugs:** Important findings have been described with respect to the role of CYP2D6 polymorphism for the clinical outcome of psychoactive drugs. Depending on the pharmacokinetic and pharmacodynamic properties of the administered drug, the impact of the functionality of the enzymes differs. The increased concentration of the parent drug or its active metabolites can result in an increased risk of toxicity or loss of therapeutic effect in PMs. On the other hand, UMs of CYP2D6 might require higher doses than recommended in order to achieve therapeutic drug levels. In one typical example, a patient was found to require high doses of nortriptyline (300–500 mg per day) to achieve “therapeutic” plasma levels (200–600 nM).\(^{108}\) A debrisoquine phenotyping test confirmed that this patient was an UM of debrisoquine and nortriptyline with a metabolic ratio of 0.07. This metabolic ratio was one of the lowest seen in a Swedish population. In 1993, 8 years later, this patient was genotyped and found to have a duplication of the CYP2D6 gene and thus three functional genes, leading to an increased activity of the enzyme.\(^{109}\)

Dalen et al.\(^{103}\) gave single oral doses of nortriptyline to healthy Swedish subjects with different numbers of active CYP2D6 alleles (Fig. 3). As expected the highest concentration of the parent drug was seen in subjects with zero active genes, i.e., PMs. The lowest concentration was seen in a subject with 13 genes (Fig. 3, left). The concentration of the 10-hydroxymetabolite were highest with 13 genes and lowest in PMs (Fig. 3, right). This demonstrates a clear gene-dose relationship.\(^{103}\)

Between UMs and PMs, we have individuals classified as EMs. Morita et al.\(^{110}\) showed the influence of the CYP2D6*10 allele on the steady state plasma levels of nortriptyline and its 10-hydroxy metabolite in Japanese depressed patients. CYP2D6*10 encodes an enzyme with decreased activity to metabolise nortriptyline. This effect is less pronounced than that of the CYP2D6*4 allele, which encodes no enzyme at all. Genotyping or phenotyping for CYP2D6 may be a tool to predict proper initial dosing of drugs such as nortriptyline in individual patients, especially those with extremely low or high CYP2D6 activity. This can be demonstrated with our experience with two patients for whom the dosage of nortriptyline and other antidepressants needed to be individualized.

The meta-analysis performed by Kirchheiner et al.\(^{111}\) reveals that the dosage of about 50% of antidepressants used is very dependent on the CYP2D6 genotype and is most important. In a study of 100 consecutive psychiatric inpatients genotyped for CYP2D6 on admission, the number of adverse effects in patients treated with CYP2D6 substrates was highest in PMs and higher in intermediate metabolisers (IMs) than in EMs or UMs.\(^{112}\)

With respect to the treatment of schizophrenia with perphenazine, thioridazine or haloperidol, significant over-sedation has been found to be linked to the CYP2D6 genotype in three different studies. Increased frequency of Parkinsonism was seen in two studies as reviewed by Dahl,\(^{113}\) whereas no significant relationship has been seen

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**Fig. 2.** Graphical presentation of drug levels achieved in predicted phenotype of CYP2D6 from different alleles of CYP2D6

Parent drug: An active drug per se. Pro-drug: An inactive drug, converted into an active metabolite.
to tardive dyskinesia, acute dystonia, or akathisia. The relationship to Parkinsonism has also been documented in several other studies. For example, in an investigation where 77 patients prescribed CYP2D6-dependent antipsychotic drugs and 55 patients prescribed non-CYP2D6 dependent antipsychotic drugs were studied, it was revealed that PMs were four times more likely to start with antiparkinsonian medication.114 Drugs against parkinsonian side effects were given twice more frequently in PMs among 241 psychiatric patients.115

In a thorough study it was found that haloperidol clearance correlated with the number of active CYP2D6 genes. Ratings for pseudoparkinsonism were higher in PMs and a trend towards lower therapeutic efficacy with increasing number of active CYP2D6 genes was seen. In addition, genotyping was as good predictor of adverse drug reactions (ADRs) as measurements of drug concentrations.116 Side effects among PMs have often been registered. In addition, nonresponsiveness to antidepressant therapy is a serious problem and has been found to be associated with the multi/duplicated copies of CYP2D6 in a pilot study.117 Subjects who were UMs were highly over-represented in the non-responder group as compared to the control population. The association of UMs and nonresponders to antidepressants requires further prospective studies especially in the Mediterranean area where the frequency of CYP2D6 gene duplications is much higher than in Northern Europe.98

Genotyping for CYP2D6 in psychiatric patients might be useful to diagnose PM and UM patients treated with antidepressant or neuroleptic drugs. A combination of genotype and phenotype i.e., determination of plasma drug concentration would be recommended. A low plasma concentration of nortriptylline or haloperidol could be due to CYP2D6 gene duplication or poor compliance. This may be shown by the presence or absence of multiple CYP2D6 genes.

CYP2D6 and treatment of cardiovascular disorders: Studying CYP2D6 polymorphism in cardiovascular patients has relevance because this enzyme metabolises 30 to 50 drugs,118 many of which are cardiovascular drugs. In PMs such drugs would often be handled as a low intrinsic clearance drug with the oral bioavailability markedly increased and the half-life prolonged. This would be reflected by increases in the peak plasma concentrations after oral dosing and increases in the steady state plasma concentrations during chronic dosing.

Several drug substrates of the polymorphic enzyme are also sometimes used concurrently in patients with cardiovascular diseases, and the treatment results in many such situations may not be or would be difficult to be monitored by objective parameters. Goryachkina et al.119 investigated patients with an acute myocardial infarction treated with metoprolol, a typical CYP2D6 substrate. When such patients developed a depression, they were co-treated with paroxetine, a potent inhibitor of CYP2D6. Paroxetine inhibited the metabolism of metoprolol and potentiated its effects by increasing the maximum concentration of both S- and R-metoprolol.120

Furthermore, patients with cardiovascular diseases are generally older than 50 years and many are more than 65 years. In older patients, complications from pharmacotherapy constitute a highly significant health problem. Adverse reactions to drugs of all types are seven times higher in those aged 70 to 79 years than in those who are 20 to 29 years old121 and concomitant administration of interacting drugs would be expected to add to the problems. Cases of drug-drug interaction were reviewed in a group of 100 elderly patients with an average of more than 5 prescribed drugs. Eighty percent of the patients had at least 1 incidence of drug-drug interaction and 22.7% of the cases were due to concurrent use of CYP2D6 substrates or inhibitors.122 Drugs used in cardiovascular patients are also usually for a long-term therapy and adverse reactions may be increased especially when patients also go on their own to use over the counter drugs (OTC)123 and probably herbal medicines which may be CYP2D6 substrates or inhibitors. For example, berberine, which is a plant alkaloid widely

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Fig. 3. Mean plasma concentrations of nortriptyline (left) and 10-hydroxynortriptyline (right) in different CYP2D6 genotype groups after a single oral dose of nortriptyline

The numerals close to the curves represent the number of functional CYP2D6 genes in each genotype group. In groups with 0–3 functional genes, there were five subjects in each group while there was only one subject with 13 functional genes. Reproduced with permission from Dalén et al.103
used to treat gastrointestinal infections, diabetes, hyper-
tension, and hypercholesterolemia, has been found to
decrease CYP2D6, 2C9, and CYP3A4 activities.124

Further suggestions on the importance of the genetic
polyorphism of drug metabolizing enzymes on cardio-
vascular diseases can be seen from studies such as that of
Thum and Borlak’s.125 These authors investigated the
gene expression of major human cytochrome P450 genes
in the heart. They found that mRNA for CYP2D6 was
predominantly expressed in the right ventricle. A strong
correlation between tissue-specific gene expression and
enzyme activity was also found.

Monohydroxylation of the antianginal agent perhexiline is
almost exclusively catalysed by CYP2D6 with activities
being about 100-fold lower in CYP2D6 PMs than in EMs.126
Perhexiline has a concentration-related hepatotoxicity and
peripheral neuropathy and determination of the CYP2D6
genotype will predict dose requirements and reduce the
risk of perhexiline concentration-related toxicity.127

In a retrospective study, Wuttke et al.128 identified 24
patients treated with metoprolol who had experienced
pronounced adverse effects. Genotyping revealed a five-fold
higher frequency of PMs in this group (38%) as compared
to the control population. As many of the drugs used to
treat cardiovascular diseases have a wide therapeutic
window, the impact of CYP2D6 polymorphism becomes
less significant. As expected, CYP2D6 genotype-phenotype
correlates with differences in metoprolol pharmacokinetics
with 30-fold variability in area under the curve (AUC)
among EMs. However, there was no association between
variable pharmacokinetics or CYP2D6 genotype and β-
blocker-induced adverse effects or efficacy.129

**Genetic polymorphism of CYP2D6 and tamoxifen:**
Genetic polymorphisms of CYP2D6 have been reported as
the major cause of variation in the metabolism of tamoxifen
that leads to adverse effects or lack of therapeutic efficacy.
The US Food and Drug Administration (FDA) advisory
committee has recommended labeling changes to indicate
that post-menopausal estrogen receptor (ER) positive breast
cancer patients who are taking adjuvant tamoxifen and are
homozygous CYP2D6*4/*4 have significantly decreased
relapse-free survival compared to those with the hetero-
zygous or homozygous wild type of CYP2D6.130,131 However
the FDA has not recommended routine testing of all women
on tamoxifen for risk stratification. In addition, there were
no comments on the impact of several variants such as
CYP2D6*5,*10, and *41 and ethnic variation. Wide inter-
patient variations in responses to tamoxifen have been
observed across populations where administration of the
same dose of this drug results in a range of outcomes which
include adverse events or therapeutic failure. Among
Caucasians, tamoxifen-treated patients carrying the hetero-
zygous and homozygous CYP2D6*4 had a significantly
increased risk of recurrence of breast cancer, shorter
relapse-free periods and worse event-free survival rates
compared with carriers of functional alleles.130,131 A recent
study among breast cancer patients with CYP2D6*10/*10 in
Asians has shown that the steady state plasma levels of 4-hydroxytamoxifen and endoxifen were significantly lower.
In addition, breast cancer patients with CYP2D6*10/*10 had significantly shorter median time to disease progression
compared to patients who were homozygous wild-type or
heterozygotes.132–134 Furthermore, breast cancer patients
who received adjuvant tamoxifen therapy revealed worse
therapy outcomes in patients with the CYP2D6*10/*10
genotype and significantly higher incidence of recurrence
within 10 years after the operation.133,135 In a Japanese
study, women who had the CYP2D6*10/*10 genotype had
a significantly higher incidence of recurrence within 10
years compared to women with the wild type genotype
(CYP2D6*1/*1). Patients with genotype CYP2D6*10/*10
showed shorter recurrence-free survival relative to the wild
type (CYP2D6*1/*1). The results of a Chinese study of 152
women with breast cancer receiving tamoxifen were also
supportive.130 The study observed that the serum levels of
4-hydroxy-tamoxifen were reduced in patients bearing
the homozygous CYP2D6*10/*10 genotype relative to the
wild type. They also observed that disease-free survival was
reduced in tamoxifen-treated women who had CYP2D6*10/
*10 genotype expression relative to wild type.

In a Dutch population, the risk of death due to breast
cancer was significantly increased in tamoxifen users with the
CYP2D6*4/*4 genotype. The CYP2D6*4 polymorphism
affects breast cancer survival in tamoxifen users.136 In
multi-variate models that adjusted for age, race/ethnicity,
educational status, method of referral into the study,
and prior knowledge of CYP2D6 testing, the patients’
CYP2D6 genotype was found to be the only significant
factor that predicted a change in the choice of hormonal
therapy.137

Kiyotani et al.138 evaluated the usefulness of knowledge
of CYP2D6 genotypes in 98 Japanese breast cancer patients
who had been taking 20 mg of tamoxifen daily as an
adjuvant setting. For the patients who had one or no
normal allele of CYP2D6, dosages of tamoxifen were
increased to 30 and 40 mg/day, respectively. Dose adjust-
ment was found to be appropriate in the patients carrying
the CYP2D6*10 allele to maintain an effective endoxifen
level. These findings are important to predict the effect-
iveness and resistance of tamoxifen therapy among breast
cancer patients. These lines of evidence also imply that pre-
genotyping of CYP2D6 intermediate metaboliser is impor-
tant before prescribing tamoxifen. These results confirmed
the findings of previous studies and support FDA
recommendation to perform pre-genotyping in patients
before the choice of therapy is determined in breast cancer
patients. In contrast, two studies from Japan showed that
the CYP2D6*10/*10 genotype was unlikely to have any
clinical significance on breast cancer patients receiving
adjuvant tamoxifen.139,140

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CYP2D6 And Drug Interactions and Clinical Implication

As CYP2D6 plays an important role in the metabolism of at least 25% of the marketed drugs, there are possible issues of drug interactions in vivo which are of clinical significance. Substrates with a high affinity bind strongly to CYP2D6 and would result in inhibition of the metabolism of other compounds which have lower affinity. Consequently, drug interactions occur in EMs, but not in PMs as they do not have CYP2D6 enzymes to compete for. Another issue that requires attention is phenocopying, whereby an EM would be phenotypically poor if he was concurrently prescribed a strong inhibitor of CYP2D6. The first pass metabolism of the substrate might be inhibited and the rate of elimination prolonged resulting in higher plasma concentration and toxicity. On the other hand, inhibition of metabolism by CYP2D6 causes lack of therapeutic response when the pharmacological action is dependent on the transformation of pro-drugs to active metabolites. Since CYP2D6 is not inducible, drug interactions due to enzyme induction are very unlikely to occur.

Several drugs have been used concurrently in clinical situations and impair the metabolism catalysed by CYP2D6. Potent inhibition of CYP2D6 has been observed when selective serotonin reuptake inhibitors (SSRIs) are used to reduce hot flushes in women with breast cancer, but results in decreased plasma concentrations of the active metabolite endoxifen. Thus the use of the SSRIs that are potent CYP2D6 inhibitors (e.g., paroxetine and fluoxetine) concurrently with tamoxifen may be associated with poorer outcomes and should be avoided as far as possible. The NCCTG 89-30-52 trial analysed the co-prescription of CYP2D6 inhibitors and CYP2D6 metaboliser status and concluded that the clinical benefit of tamoxifen was significantly decreased in patients with decreased CYP2D6 activity either due to the PM genotype or the concurrent use of CYP2D6 inhibitors. In addition to drug-drug interaction, cautious use of herbal medicine should be practiced to avoid drug-herb interactions. For example, the alkaloids protopine and allocryptopine in black cohosh were identified as competitive CYP2D6 inhibitors and thus should be used with caution in breast cancer patients treated with tamoxifen. Similarly, concurrent use of Hypericum extract should be avoided in patients treated with SSRIs.

In 2000 Hamelin et al. reported interaction of non-prescription drugs with CYP2D6 substrates. There was a 61% increment in the AUC of metoprolol when diphenhydramine was co-administered in EMs. A significant aggravation of metoprolol-related effects such as decrease in heart rate, systolic blood pressure, and Doppler-assessed aortic blood flow was observed after administration of diphenhydramine. Even though metoprolol has a wide therapeutic window, the interaction can be severe especially because many older patients with multiple co-morbidities take both of these drugs simultaneously.

CYP2D6 and Disease Susceptibility

The CYP2D6 phenotype and genotype has been investigated with respect to the risk of cancers and other diseases. Individuals who were EMs because of CYP2D6 had higher risks of malignant processes as increased metabolism of one or more agents in the diet or other environmental agents, mediated by CYP2D6, forms reactive intermediaries that influence the initiation or promotion of cancer in various tissues. It has been found that polymorphism at loci that encode carcinogen-metabolizing enzymes such as cytochrome P450, which catalyzes the detoxification of carcinogens, may determine susceptibility to cancer. On the other hand, PMs must be exposed longer to the toxic effects of non-metabolised drugs and numerous other factors to have increased risks of cancers. The types of cancer that were evaluated included melanoma, lung-, breast-, anogenital-, basal cell- aerodigestive tract-, oral-, prostate-, pancreatic- and bladder-cancer. Association was observed between the CYP2D6 gene and lung cancer, bladder cancer, and oral cancer. London et al. found that the CYP2D6 genetic polymorphism is not a strong risk factor for lung cancer. Smith et al. and Goetz et al. stated that CYP2D6 genotype is not the causal factor for breast cancer. Meanwhile, reduced CYP2D6 activity (PM) has been related to greater risk of leukemia and oral cancer. There is however a lack of consistency in the results observed, and a clear distinction between the EM and PM phenotypes with regard to susceptibility to cancer cannot be established.

CYP2D6s are found in the brain and they are similar to those found in the liver and thus studies have attempted to associate their role with CNS disorder. Researchers hypothesized that CYP2D6 may play an essential role in the biological activity as it is expressed in the brain. In fact, two studies have indicated a significant relationship between CYP2D6 and behavior, using psychological tests and the presence of CYP2D6. It was shown that there was a higher number carrying more than two active CYP2D6 genes (gene duplication) among those who died of suicide (suicide cases), as compared with those who died of natural causes (natural-death cases) (p = 0.007). It was suggested that CYP2D6 transforms 5-methoxy tryptamine to serotonin in the brain of suicide attempters. Several studies have indicated serotonergic hypofunction in suicidal behavior. These studies suggest that CYP2D6 in the human brain is important for behavior.

Interestingly, Pai et al. have provided evidence that a common variant of the pseudogene CYP2D7 could be expressed in an active form in human brain yielding a functional enzyme that is active in the metabolism of codeine. Allelic variation at the CYP2D6 gene has been suggested to be associated with CNS disorders, includ-
ing Parkinson’s disease (PD), Lewy body dementia and Alzheimer’s.\textsuperscript{158} Poor CYP2D6 metabolisers were are at higher risk for PD due to their reduced ability to inactivate PD-causing neurotoxins. Patients with PD cases had approximately 40% lower CYP2D6 levels in the frontal cortex, cerebellum, and hippocampus.\textsuperscript{159}

However, the CYP2D6 genotypes related disease risk are conflicting due to the small sample size and the heterogeneous nature of the diseases, the sampling and nature of age-matching, and the polygenetic nature of these diseases.\textsuperscript{160} In addition, the genotypes screened in each study may be limited and not comprehensive enough to provide conclusive data.

**Conclusion**

CYP2D6 is highly polymorphic and heterogeneous. The type and frequencies of alleles show ethnic specificities. The clinical impact of genetic polymorphism of drug metabolism enzymes is higher in drugs with a narrow therapeutic window and only one metabolic pathway is involved with more than 90% of the metabolism. Many of the drugs today are designed to share more than one drug metabolizing enzyme. This would increase the market population as severe toxicity due to impaired functionality of one enzyme would be reduced. However, toxicity due to drug interaction may occur due to phenocopying and special attention is required. Thus far, pre-genotyping of CYP2D6 before drugs are prescribed is recommended for tamoxifen, antidepressants and antipsychotics to identify those special patients who may need to have the dosage adjusted. In Caucasians, the risk of adverse effects due to poor metabolism would be higher than in Asians.

Asians have a lower capability to metabolise CYP2D6 substrates but as most of the CYP2D6 substrates do not have narrow therapeutic windows, the clinical impact is less obvious. However, if the drugs are for chronic dosing, accumulation may occur and result in toxicity.

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