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REVIEW

# CYP2D6 polymorphisms and their influence on risperidone treatment



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**Abstract:** Cytochrome P450 enzyme especially *CYP2D6* plays a major role in biotransformation. The interindividual variations of treatment response and toxicity are influenced by the polymorphisms of this enzyme. This review emphasizes the effect of *CYP2D6* polymorphisms in risperidone treatment in terms of basic knowledge, pharmacogenetics, effectiveness, adverse events, and clinical practice. Although the previous studies showed different results, the effective responses in risperidone treatment depend on the CYP2D6 polymorphisms. Several studies suggested that *CYP2D6* polymorphisms were associated with plasma concentration of risperidone, 9-hydroxyrisperidone, and active moiety but did not impact on clinical outcomes. In addition, CYP2D6 poor metabolizer showed more serious adverse events such as weight gain and prolactin than other predicted phenotype groups. The knowledge of pharmacogenomics of *CYP2D6* in risperidone treatment is increasing, and it can be used for the development of personalized medication in term of genetic-based dose recommendation. Moreover, the effects of many factors in risperidone treatment are still being investigated. Both the *CYP2D6* genotyping and therapeutic drug monitoring are the important steps to complement the genetic-based risperidone treatment.

**Keywords:** *CYP2D6*, risperidone, polymorphisms, adverse drug reaction, pharmacogenetics, pharmacokinetics, pharmacodynamics

## Introduction

Risperidone is an atypical antipsychotic (AAP) drug that is being prescribed for the treatment of irritability or aggression in autism, schizophrenia, and acute bipolar mania. Risperidone exerts its pharmacologic effects by binding to and inhibiting high-affinity serotonin and dopamine receptor.[1] As a result, treating these symptoms can reduce the disease severity and thus can improve quality of life of patients. Risperidone is metabolized by hepatic metabolism via the CYP2D6 enzymatic pathway to its major active metabolite, 9-hydroxyrisperidone or paliperidone, which has pharmacologic effects equivalent to those of risperidone. Therefore, therapeutic response on risperidone administration is the total of the active moiety of plasma risperidone and 9-hydroxyrisperidone concentrations. There are evidences of various differences in risperidone treatment in different individuals, which may explain the pharmacologic activity between risperidone and 9-hydroxyrisperidone that further explains the difference in clinical outcomes of *CYP2D6* genetic polymorphisms. To date, >100 allele variants of *CYP2D6* genotype have been proposed and predicted in 4 different phenotypes: extensive (normal activity), intermediate (reduced activity), poor (no activity), and ultra-rapid (high activity) metabolism.

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Because the long-term use of these psychotropic medications may cause some adverse effects,[2] various concerns arise regarding the health implications of its side effects as well as its medication compliance, which lead to symptom relapse which is a common challenge in clinical management of psychiatric disorder.[3] Pharmacogenetic testing can thus help predict the response or probability of adverse effects and optimize the clinical decisions. Therefore, the objective of this review was to summarize and evaluate the pharmacogenetic effects of *CYP2D6* polymorphism on risperidone therapy, both efficacy and adverse drug reaction (ADR), including insights for the potential impact of this field on the safe and effective use of medications with future prospects and challenges.

## Pharmacokinetic and pharmacodynamic profile of risperidone

### Pharmacokinetics

Risperidone has the property of being well absorbed. The absolute oral bioavailability of risperidone is ~70%. The relative oral bioavailability of risperidone from a tablet is 94% when compared to that from a solution. Risperidone is rapidly distributed, and the volume of distribution is 1–2 L/kg. The major active metabolite is 9-hydroxyrisperidone (paliperidone); both are the substrates of the drug transporter P-glycoprotein (P-gp). Thus, P-gp affects both the absorption and brain concentrations of this drug. A study in mouse model showed the effect of P-gp in total brain-to-plasma (B/P) ratios of risperidone and its active metabolite. The brain concentrations and B/P ratios of risperidone (13.1-fold and 12-fold) and 9-hydroxyrisperidone (29.4-fold and 29-fold) were significantly higher in the *ABCB1* knockout mice than wild-type mice.[4] The other mouse models show similar results. The B/P ratios of risperidone and its active metabolite 9-hydroxyrisperidone (10-fold and 17-fold) were significantly higher in knockout mice than wild-type mice and also correlate with cerebrospinal fluid/plasma ratios (6.3-fold and 9.3-fold).[5] These results indicate that P-gp in the blood–brain barrier significantly influences the brain concentrations of risperidone and 9-hydroxyrisperidone.

Risperidone is greatly metabolized in the liver by cytochrome P450 2D6 enzymes (CYP2D6). An active metabolite by main hydroxylation pathway is 9-hydroxyrisperidone. Another minor metabolic pathway is through N-dealkylation. An in vitro study of several human cytochrome P450 (CYP) enzymes showed the activity on the metabolism of risperidone such as CYP1A1, CYP1A2, CYP2C8, CYP2C9-arg144, CYP2C9-cys144, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes. Three CYP enzymes, CYP2D6, CYP3A4, and CYP3A5, showed the main activity of metabolizing risperidone to 9-hydroxyrisperidone, with activities of 7.5, 0.4, and 0.2 pmol $pmol^{-1}$ CYP $min^{-1}$, respectively. Moreover, a study on human liver microsomes showed high correlation in the activities of CYP2D6 and CYP3A in the formation of 9-hydroxyrisperidone. This result is confirmed by using inhibitors of CYP2D6 (quinidine) and CYP3A4 (ketoconazole) to inhibit the formation of 9-hydroxyrisperidone. Thus, both CYP2D6 and CYP3A4 are the main enzymes for the metabolism of risperidone to 9-hydroxyrisperidone.[6]

### Pharmacodynamics

Risperidone is the dopamine, $D_1$ ($D_1$, $D_5$) and $D_2$ family ($D_2$, $D_3$, and $D_4$), receptor antagonist. Moreover, it also has a high-affinity antagonist effect for the serotonin type 2 ($5HT_2$), $\alpha_1$ and $\alpha_2$ adrenergic, and $H_1$ histaminergic receptors.[7] The antagonist effects were found in both in vitro and in vivo studies.[8,9] Furthermore, new mechanism as partial uncompetitive inhibition on D-amino acid oxidase (DAO) was investigated. The results showed a protective effect of risperidone from D-amino acid-induced cell death. The new antischizophrenia mechanism of risperidone has been proposed.[10] Risperidone blocks the mesolimbic pathway, the prefrontal cortex limbic pathway, and the tuberoinfundibular pathway in the central nervous system. These pathways can increase the secretion of prolactin causing sexual side effects, such as galactorrhea, infertility, and gynecomastia.

Risperidone has high affinity for the serotonin type 2 (5HT2A, Ki of 0.6 ± 0.2 nM and 5HT2C Ki of 26 ± 5 nM) and dopamine type 2 (D2, Ki = 3 ± 1 nM) and type 4 (D4, Ki = 7 ± 1 nM). Whereas, low to moderate affinity for serotonin type 1 (5HT1A, 5HT1C, and 5HT1D, Ki of 100–1325 nM) and dopamine type 1 (Ki = 75 nM) and no affinity for cholinergic muscarinic receptors have been observed (inhibition of binding <50% at concentrations 10,000 nM).[11]

Other binding affinity studies also showed the similar result.[12] Risperidone and its metabolite showed the potent binding at 5HT2A (Kd = 0.15 ± 0.02 nM and 1.21 ± 0.06 nM), 5HT2C (Kd = 32 ± 4 nM and 48 ± 5 nM), D2 (Kd = 3.77 ± 0.04 nM and 2.8 ± 0.3 nM), α1 (Kd = 2.7 ± 0.3 nM and 10.1 ± 0.8 nM), α2 (Kd = 8 ± 1 nM and 80 ± 10 nM), and H1 histaminergic receptors (Kd = 5.2 ± 0.5 nM and 3.4 ± 0.4 nM), respectively. However, low-affinity binding of risperidone and 9-hydroxyrisperidone was found not only with 5HT1A (Kd = 190 ± 20 nM and 480 ± 40 nM) but also with muscarinic receptor (Kd of 34,000 ± 3000 nM and

8800 ± 500 nM).[12] The pathway of pharmacokinetics and pharmacodynamics of risperidone was shown in Figure 1.

## Interethnic variation of *CYP2D6* alleles across world populations

CYP2D6 is the major enzyme in metabolism of many prescribed drugs (Table 1). The *CYP2D6* gene is located on chromosome 22 (22q13.1) and is composed of 9 exons with an open reading frame of 1491 base pairs coding for 497 amino acids and 8 introns.[13–16]

Data on allelic distribution worldwide, modified from Hick et al[17] (Table 2) showed that the frequencies of *CYP2D6* allele with nonfunctional enzyme activity, that is, *CYP2D6*3*, **4*, and **5* (gene deletion), are higher in Caucasian, American, African, and Middle East population and also found high allelic frequency in South/Central Asian. *CYP2D6*4* (1846G>A, rs3892097) is the most frequent variant allele in European/Caucasian or European/North American population in ~18.0% (minimum–maximum: 8.1%–33.4%) and present in 70%–90% of all nonfunctional phenotypes.[15,18] Moreover, *CYP2D6*36* which is gene conversion (GC) or hybrid between *CYP2D7* pseudogene and *CYP2D6* (*CYP2D6-2D7*) in exon 9 results in nonfunctional CYP2D6 enzyme activity.[19] *CYP2D6*36* has rare frequency in almost of all the populations except Asian population; the highest allelic frequency of **36+*10* in Japanese which investigated and reported by Hosono et al[20] and Kiyotani et al[21] was ~24.2% and 32.7%, respectively. *CYP2D6*17* has the most frequent, reduced enzyme activity in African (20%, 9%–34%), and *CYP2D6*41* (2988G>A, rs28371725) allele with decreased enzyme activity showed the highest allele frequency in Middle East (20%, 15.2%–29%) and African (10.9%, 1.4%–25.3%). However, allele with decreased enzyme activity, especially *CYP2D6*10* (100C>T, rs1065852), has highest frequencies in Asian population, especially Thai (~50%)[22–26] and East Asian (~42.7%)[17] populations, but it is rare in Caucasian.[27–29] In a previous study by our group, it was found that the data of allele distribution resemble that in East Asian populations but differ from other populations. Many tools were used for the detection of *CYP2D6* genotyping, that is, microarray, allele specific primer extension (ASPE) (bead array), and TaqMan single-nucleotide polymorphism (SNP) genotyping along with TaqMan CNV kit. Perhaps, the different allele distribution of *CYP2D6* gene may depend on several techniques that

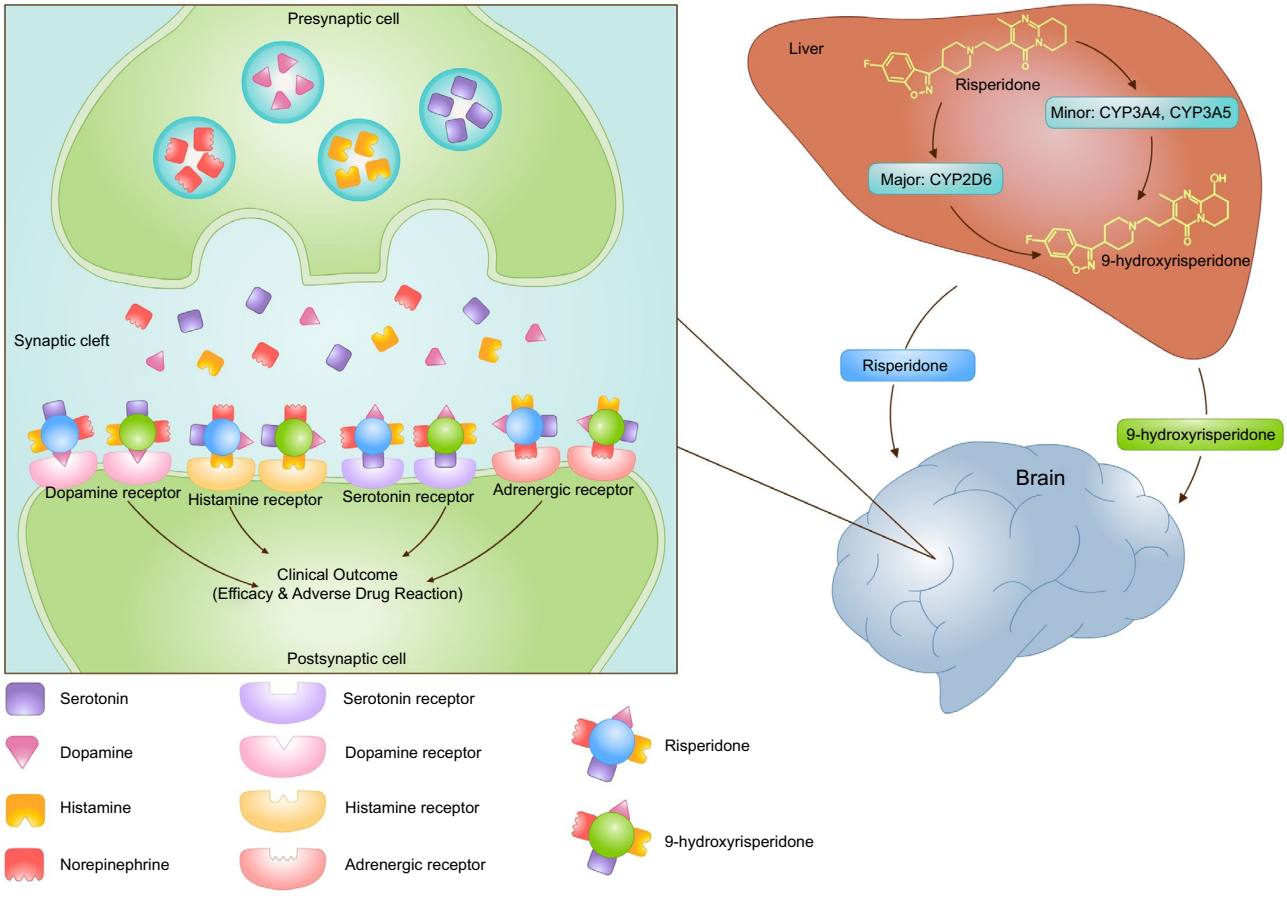


**Figure 1** The pathway for pharmacokinetics and pharmacodynamics of risperidone.

**Table 1** Clinically relevant drug substrates for metabolism by CYP2D6 enzymes

| CYP2D6 substrates | | | | | |
|---|---|---|---|---|---|
| **Antidepressants** | **Beta blockers** | **Anti-cancer** | **Antipsychotics** | | |
| Amitriptyline | Alprenolol | Tamoxifen | Haloperidol | Mexiletine | Methoxyamphetamine |
| Clomipramine | Carvedilol | | Perphenazine | Minaprine | Bufuralol |
| Desipramine | Propafenone | | Risperidone | Nebivolol | Chlorpheniramine |
| Imipramine | Bupranolol | | Thioridazine | Nortriptyline | Chlorpromazine |
| Fluoxetine | Clonidine | | Zuclopenthixol | Ondansetron | Clonidine |
| Paroxetine | Debrisoquine | | Atomoxetine | Oxycodone | Codeine |
| Tamoxetine | Metoprolol | | Alprenolol | Perhexiline | Debrisoquine |
| Trimipramine | Propranolol | | Amphetamine | Phenacetin | Dexfenfluramine |
| Venlafaxine | Timolol | | Aripiprazole | Phenformin | Dextromethorphan |

are used for detection in each laboratory besides the diverse ethnic groups. Interestingly, there are many rare alleles that have not yet been determined or could not be performed by the current assay such as **18*, **21*, **27*, **28*, **33*, **39*, **43–*55*, **60*, **63*, **65*, **69*, **75*, and so on. Thus, the data of other rare or novel alleles which can be found in many populations around the world including Thai population might be missed. In addition, the samples in each study had many different genetic background or diseases, some were healthy volunteers whereas others suffered from many diseases such as breast cancer, sickle cell anemia, psychiatric, fatal intoxication cases, and so on, which affected the distribution of the allele frequency.

## "Predicted" phenotypes and "measured" metabolic phenotypes on medication

Identification of allele depends on the changes in nucleotides or mutations which affect the changes in amino acid, which subsequently affect the changing protein structures and the characterization of enzyme activity including increased, decreased, and no enzyme activity that need to be determined in both in vitro and in vivo studies in order to confirm the exact enzyme activity. There are many functional CYP polymorphism patterns that result from the SNPs, that is, synonymous and nonsynonymous SNPs, nucleotide substitution, frameshift, splicing defect, *CYP2D7/2D6* hybrid or GC, small insertion/deletion, tandem rearrangement, especially gene deletion, duplication, and multiplication. These variations of *CYP2D6* gene could change protein function. Not only variants in the regions of exon protein coding are found, which is most important to amino acid changes, but also the data of mutations in all the regions of the gene including intronic, intergenic, promoter, and untranslated region (UTR)[30,31] as well as *CYP2D7/2D6* hybrid gene in both exon and intron regions are revealed.[32] The significant alteration of polymorphisms in *CYP2D6* gene produces various forms of enzyme activity and biotransformation pathway of the currently prescribed drugs in clinical treatment.[33] The variations of *CYP2D6* genotype–phenotype were defined as active, inactive, reduced, and increased functional enzyme activity.

Examples of genotype–phenotype relationship on drug metabolism were summarized in Table 3. Many prescription drugs in the current clinical treatment are related to the biotransformation pathway of CYP2D6 enzyme. Anticancer drug, tamoxifen (selective estrogen receptor modulator), is a pivotal adjuvant drug in breast cancer therapy. As known to the scientists for a long time, tamoxifen was metabolized by CYP2D6 to endoxifen, N-desmethyl-tamoxifen, and so on, which has more potent binding affinity with estrogen receptor.[34] Hertz et al[35] revealed that tamoxifen, a prodrug in the adjuvant treatment of breast cancer patients, was metabolized by CYP2D6 enzyme to its metabolite (endoxifen) and that the patients who carried IM (EM/IM, EM/PM, IM/IM, IM/PM) or PM (PM/PM) phenotype had reduced median endoxifen concentration compared with EM (EM/EM) phenotype.

Most of the antidepressant drugs were metabolized via CYP2D6 enzyme. Several previous studies used antidepressant drugs as model of transformable genotype to potential phenotype and showed the significantly different area under the concentration time curve (AUC) of nortriptyline drug among the patients who carried PM; IM phenotype had higher AUC than patients who carried EM phenotype (Table 3).[36–37] Thus, the challenges of predicted phenotype used in clinical treatment depend on individual drug substrates and ethnic population samples.

In the case of risperidone treatment in autistic spectrum disorder, Novalbos et al[38] reported that the metabolic ratio (MR) of the AUC for risperidone and 9-hydroxyrisperidone of patients with PM and IM had significantly different MR from EM. Furthermore, most of the pharmacokinetic parameters (AUC, $C_{max}$, $T_{max}$, $t_{1/2}$, and Cl/F) of risperidone

**Table 2** Frequency of *CYP2D6* alleles[a] by using AmpliChip platform in different ethnic groups

| *CYP2D6* alleles | Thai[b] (%) | Thais (%) | | | | Thais (%) | East Asian (%) | South/Central Asian (%) | Middle East (%) | Oceania (%) | Caucasian (%) | American (%) | African (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N=255 | Chamnanphon et al[22] (N=57) | Vanwong et al[25] (N=84) | Sukasem et al[84] (N=147) | Suwannasri et al[24] (N=288) | Average | | | | | | | |
| *1 | 27 | 35 | 28 | 32.3 | 22.9 | 29 | 34.2 | 53.7 | 58 | 70.2 | 39 | 52.0 | 32.8 |
| *2 | 8.6 | 9.6 | 5.9 | NA | 9.7 | 9.9 | 12.8 | 31.9 | 21.7 | 1.2 | 28.1 | 22.9 | 20.1 |
| *3 | 0 | 0 | 0 | 0 | NA | 0 | 0 | 0.03 | 0.08 | 0 | 1.33 | 0.62 | 0.03 |
| *4 | 1.2 | 0.9 | 1.2 | 1.7 | 0.7 | 1.1 | 0.4 | 6.6 | 7.8 | 1.1 | 18.0 | 10.7 | 3.4 |
| *5 | 5.1 | 4.4 | 8.3 | 6.1 | 4.3 | 5.6 | 5.6 | 2.5 | 2.3 | 5 | 2.8 | 1.9 | 6.1 |
| *10 | 52.6 | 45.6 | 51.8 | 55.1 | 44.6 | 50 | 42.3 | 19.8 | 3.5 | 1.6 | 2.9 | 2.8 | 6.8 |
| *14 | 0.9 | 0.9 | 0 | NA | 1.04 | 0.71 | 0.9 | 0 | 0 | 0 | 0 | 0.3 | 0.3 |
| *17 | 0 | 0 | 0 | NA | NA | 0 | 0.01 | 0.2 | 1.6 | 0.05 | 2.9 | 2.3 | 20.0 |
| *29 | 0 | 0 | 0 | NA | NA | 0 | 0 | 0.1 | 0.8 | 0 | 0.1 | 1.4 | 10.3 |
| *35 | 0.5 | 0.9 | 0 | NA | NA | 0.5 | 0.2 | NA | 2.0 | 0 | 5.8 | 2.0 | NA |
| *36 | 0.9 | 0.9 | NA | NA | 16.4 | 6.1 | 1.6 | NA | 0 | 0 | 0 | 0.3 | 0 |
| *41 | 3 | 1.8 | 3.6 | 4.8 | NA | 3.3 | 2 | 10.5 | 20.4 | 0 | 7.7 | 3.9 | 10.9 |
| *XN | 0.2 | 0 | 6 | NA | 0.4 | 1.7 | 0.4 | 0.5 | 3.9 | 0 | 2.7 | 3.83 | 7.6 |

**Notes:** Data from Hicks et al.[17] [a]Nucleotide changes and enzyme activity were based on algorithm of Roche AmpliChip. [3]Average frequencies are based on the actual number of subjects with each allele reported in multiple studies. [b]Unpublished data by Chamnanphon et al (2016) (n=215). Average: all data were calculated from unpublished data by Chamnanphon et al (2016) (n=215).[22,24,25,84]

**Abbreviation:** NA, not available.

and 9-hydroxyrisperidone were significantly different in PM patients from the others (IM, EM, and UM) (Table 3).

The duplicated, multi-duplicated, or amplified *CYP2D6* genes are copy number variations (CNVs). This result exhibits increased CYP2D6 enzyme activity and leads to higher plasma drug concentration in prodrug or lower plasma drug concentration in active drugs. Furthermore, functional alterations of *CYP2D6* variants have been widely studied in the Japanese population, but the results remain inconsistent.[16,21,39,40] Cassandra Willyard et al[41] suggested that the effect of CNV in a polymorphism was studied extensively because of its close association with drug metabolism, but many scientists still overlooked the importance and influence of gene duplication, deletion, and multiplication on drug response, although CNV has been used to understand the full spectrum of human genetic variation and also to assess the significance of such variation in disease association studies. Several well-known CNV genes such as *CYP2A6*, *CYP2D6*, *GSTM1*, *GSTT1*, *SULT1A1*, *SULT1A3*, *UGT2B17*, *UGT2B7*, *UGT2B10*, and *UGT2B11* are involved in drug metabolisms.[33] However, some publications introduced the prevalence of *CYP2D6* CNV, exclusively there was less study about the significance of CNV in pharmacogenomic area. Beoris et al[42] found that 12.6% (n = 3,974/31,563) of all patients who were tested had zero (0.14%, 43), one (7.25%, 2,288), three or more copies of the *CYP2D6* gene (≥3 copy, 5.21%, 1,643) in the American population. Sheng et al[43] reported that low allele frequencies of *CYP2D6*5* and *CYP2D6*×N* were 4.82% (n=35/363) and 0.69% (n=5/363) in the Eastern Han Chinese population, respectively, and they focused on the details of duplication and multiplication including *CYP2D6*10×N* (2, 0.28%) and *CYP2D6*1×N* (3, 0.41%) and also found gene rearrangement in ~11% of all the subjects. The investigations of CNV in drug biotransformation and functional enzyme activity are unclear. However, several scientists believed that CNV is an important part of drug metabolizing enzyme; in the future, potential research studies should determine the CYP2D6 variations in order to use the accurate predicted phenotype in clinical therapy.

## Interpretation of predicted phenotype of CYP2D6 and gene activity score

Genetic variation of *CYP2D6* gene is associated with CYP2D6 enzyme activity including decreased, increased, and nonfunctional enzyme activities. The *CYP2D6* potential phenotypes include four phenotypes: poor metabolizers (PMs) lead to lack of functional enzyme activity because of

**Table 3** Relationship of *CYP2D6* genotype–phenotype on drug metabolism categorized in different drug substrates

| Potential phenotype | Example of genotype | Tamoxifen | | Potential phenotype | Antidepressant drug | | | Antipsychotic drug | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline endoxifen (ng/mL) | 4-Month endoxifen (ng/mL) | | Nortriptyline | | | Risperidone and 9-hydroxyrisperidone | |
| | | Median | Median | | AUC | AUC | AUC | Phenotype | MR (mean ± SD) |
| UM | NA | NA | NA | UM | 0.8 | | | UM | 0.08±0.03 |
| EM | EM/EM | 8.9 | 8.2 | EM | 1.3 | 1.8 | 1.7 | EM | 0.18±0.29 |
| IM | EM/IM | 7.9 | 13.1 | IM | 3.6 | 3.1 | 3.0 | IM | 0.41±0.49 |
| | EM/PM | 6.1 | 8.9 | | | | | | |
| | IM/IM | 4.3 | 6.5 | | | | | | |
| | IM/PM | 4.0 | 5.8 | | | | | | |
| PM | PM/PM | 2.4 | 6.1 | PM | 4.3 | 4.2 | 4.2 | PM | 3.41±0.67 |
| Research groups | | Hertz et al[35] | | | Dalen et al[36] | Mellstrom et al[37] | Bertilsson et al[38] | Novalbos et al[39] | |

**Abbreviations:** AUC, area under the concentration time curve in μM; EM, extensive metabolizer; IM, intermediate metabolizer; MR, metabolic ratio of the AUC for risperidone and 9-hydroxyrisperidone; NA, not available; PM, poor metabolizer; UM, ultra-rapid metabolizer; SD, standard deviation.

**Table 4** Comparison of Allele and Gene Activity Score between 3 algorithms

| AS | Gaedigk et al[44] | Crews et al[19] and Hicks et al[17] (CPIC) | Allele | Hertz et al[35] | Diplotypes | Diplotypes | Gene Activity Score | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Microarray and Bead array (ASPE) rule-based | Hertz et al[35] | Gaedigk et al[44] | Crews et al[19] and Hicks et al[17] (CPIC) |
| 0 | **3, *4, *4xN, *5, *6, *7, *16, *36, *40, *42, *56B* | **3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21,*31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62, *68, *69, *92, *100, *101* | PM | **3, *4, *5, *6, *7, *8, *11,*15, *19, *20, *40, *4xN* | 2 nonfunctional alleles | PM/PM | 0 | 0 |
| 0.5 | **9, *10, *17, *29, *41, *45, *46* | **9, *10, *14B,*17, *29, *41, *49, *50, *54, *55, *59, *72* | IM | **9, *10, *17, *29, *36, *41, *17xN, *41xN* | 1 nonfunctional allele and 1 reduced activity or 2 reduced activity alleles | EM/IM, EM/PM, IM/IM, IM/PM | 0.5–1 | 0.5 |
| 1 | **1, *2, *35, *43, *45xN* | **1, *2, *27, *33, *34, *35, *39, *45, *46, *48, *53* | EM | **1, *2, and *35* | At least 1 functional allele | EM/EM, UM/IM,UM/PM | 1.5–2 | 1–2 |
| >1 | **1xN, *2xN, *35xN* | **1xN, *2xN, *35xN, *45xN* | UM | **1xN, *2xN, *35xN* | At least 3 copies of functional allele | UM/UM,UM/EM | >2 | >2 |

**Abbreviations:** AS, activity score; CPIC, Clinical Pharmacogenetics Implementation Consortium; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer.

gene deletion or change of amino acid. Defective gene caused altered drug metabolism or would be eliminated in pharmacokinetic phase II (sulfation or glucuronidation); intermediate metabolizers (IMs) carry two reduced functional alleles or one reduced functional allele and nonfunctional allele; extensive metabolizers (EMs) carry two functional alleles or one functional allele, and this results in normal enzyme activity and drug concentration; and ultra-rapid metabolizers (UMs) carry more than two gene copies, duplicated, multiduplicated, or amplified *CYP2D6* genes. This result in enzyme activity exhibits increased CYP2D6 enzyme activity and leads to higher plasma drug concentration in prodrug or lower plasma drug concentration in active drugs.[33] The categorization of predicted phenotype or metabolizer status depends on drug probe substrates, which are challenging in each study, and it is important and difficult to translate *CYP2D6* genotyping into potential phenotype.[44] Presently, there are many different algorithms that have been used for the interpretation of predicted phenotype, and the system has not been standardized yet because of the complexity of translational genotype and accurately potential phenotype. Thus, many groups of researchers attempt to study and create new rule-based system called "Allele and Gene Activity Score" to give more detail precision and accuracy of phenotype.

## Translation of genotype into predicted phenotypes through Allele and Gene Activity Scores

Gaedigk et al,[44] Hertz et al,[35] Crew et al,[19] and Hicks et al[17] proposed classification of predicted phenotypes according to allele activity score (AS) of each algorithms according to microarray and bead array (ASPE) rule-based system. Based on these algorithms (Table 4), first, UM had at least 2 functional alleles, EM had at least 1 functional allele, IM had 1 nonfunctional allele, and 1 reduced activity or 2 reduced activity alleles, and PM had 2 nonfunctional alleles. Based on gene AS according to these studies, *CYP2D6* alleles with increased enzyme activity (i.e., **1XN*, **2XN*, **35XN*, **45XN*) were assigned to have AS as >1, alleles with normal enzyme activity (i.e., **1*, **2*, **35*) have AS as 1, alleles with reduced enzyme activity (i.e., **10, *14B*, *41*) have AS as 0.5, and alleles with nonfunctional enzyme activity (i.e., **4, *5, *36*) have AS as 0. **14B* was designated to unknown enzyme activity according to AmpliChip CYP450 rulebased, whereas reduced functional allele following *CYP2D6* allele nomenclature **36* was designated to nonfunctional enzyme activity according to Crews et al.[19] The gene activity score was the sum of the values assigned to allele 1 and 2.[107]

The assignment of predicted or potential phenotypes is based upon *CYP2D6* diplotypes. The score of *CYP2D6* diplotype is defined as gene score that combines allele score 1 and allele score 2 according to Gaedigk et al[44] and Borges et al[45] including UM (>2), EM (1.5–2), IM (0.5–1), and PM (0). In addition, several rule-based systems of allele AS had different or ambiguous alleles among many studied such as **45xN* was assigned to have the score as 1 (normal function) by Gaedigk et al,[44] whereas the score in Clinical Pharmacogenetics Implementation Consortium (Crews et al[19] and Hicks et al[17]) was assinged as >1 (increased function). *CYP2D6*36* and **36xN* were assigned score as 0 (nonfunctional) by Crews et al[19] and Hicks et al[17] in contrast to the study by Hertz et al,[35] which reported that the score of this allele as 0.5 (decreased function), and furthermore, **17xN* and **41xN* were assigned a score of 0.5. However, these models of allele and gene AS have to be validated and proved in larger group of population samples.

## Effect of CYP2D6 polymorphisms on the risperidone pharmacokinetics

Risperidone is a widely used AAP agent and has potent antagonistic properties for both dopamine D2 and serotonin-5HT2 receptors.[46] Risperidone is metabolized primarily by cytochrome P450 2D6 (*CYP2D6*) into the active metabolite 9-hydroxyrisperidone.[47] It has been believed that 9-hydroxyrisperidone had similar pharmacological activities with respect to risperidone;[48] however, recent reports suggested a different hypothesis that pharmacological activity of 9-hydroxyrisperidone might not be the same as that of risperidone. The hypothesis indicated that risperidone may be more potent and subsequently more toxic than 9-hydroxyrisperidone.[49] The totality of plasma risperidone and 9-hydroxyrisperidone levels has been stated as the total plasma active moiety, contributing to the overall therapeutic effect.[50] In terms of both efficacy and toxicity, genetic factors are generally supposed to contribute to variable treatment response.[51] Genetic *CYP2D6* polymorphism might display a high degree of interindividual variability on clinical outcome and steady state of plasma risperidone and 9-hydroxyrisperidone levels.[52]

The role of *CYP2D6* polymorphisms had been extensively reported, despite the differences in pharmacokinetics, adverse events, and clinical outcome.[29,53–55] The *CYP2D6*1*,**2*, **33*, and **35* alleles have normal enzymatic activity. *CYP2D6*10* and **41* have reduced enzymatic activity, whereas *CYP2D6*3*, **4*, and **5* have no enzymatic activity.[29,55] It was consequently reported that *CYP2D6* genotyping could be useful for assessing risperidone levels.[56] PMs had greater risperidone and total active moiety levels and lower 9-hydroxyrisperidone levels.[57] The study from healthy Chinese found that people who carry CYP2D6*10/*10 had significantly higher levels of risperidone and risperidone/9-hydroxyrisperidone ratio than those noncarriers.[58] The previous study in Autism spectrum disorders (ASD) children treated with risperidone reported that risperidone and risperidone/9-hydroxyrisperidone ratio of plasma levels was significantly higher in patients with PMs ($p$=0.03 and $p$=0.02).[59] The study in Thai ASD children and adolescents found that risperidone was significantly higher in patients with *CYP2D6*5/*10* ($p$=0.02), *CYP2D6*10/*10* ($p$=0.04), and *CYP2D6*10/*41* ($p$=0.04). However, there was no significant effect of *CYP2D6* polymorphisms on plasma concentrations of 9-hydroxyrisperidone total active moiety.[26] Vanwong et al[25] found that IM patients had higher levels of risperidone and risperidone/9-hydroxyrisperidone than EM patients ($p$=0.001 and $p$<0.0001, respectively). Moreover, the risperidone and risperidone/9-hydroxyrisperidone ratio levels in the group with CYP2D6 AS 0.5 were significantly higher than the group with the CYP2D6 AS 2.0 ($p$=0.004 and $p$=0.002, respectively).[25] Other studies in CYP2D6 polymorphism on risperidone level were shown in Table 5.

An extensive study has been performed to clarify the genetic basis of the response to risperidone in order to reduce its adverse effects.[49] The CYP2D6 genotype is an important factor for clinical treatment outcome. The dopamine

**Table 5** *CYP2D6* polymorphisms and their influence on risperidone treatment

| Study design | Total participants (n) | Subjects | Ethnicity | Genotypes | Outcome | *p*-value | References |
|---|---|---|---|---|---|---|---|
| **1. CYP2D6 polymorphisms and risperidone levels** | | | | | | | |
| Cross-sectional study | 84 | Autism spectrum disorders | Thai | *CYP2D6*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35,*41* and copy number variation | RIS and 9-OH RIS levels | RIS ($p$=0.004)<br>9-OH RIS (NS)<br>Active moiety (NS)<br>RIS/9-OH RIS ratio ($p$=0.002) | Vanwong et al[25] |
| Cross-sectional study | 97 | Autism spectrum disorders | Thai | *CYP2D6*1, *4, *5, *10* and **41* | RIS and 9-OH RIS levels | RIS ($p$<0.05)<br>9-OH RIS (NS)<br>Active moiety (NS)<br>RIS/9-OH RIS ratio ($p$=0.004) | Vanwong et al[26] |
| Observational cohort study | 40 | Autism spectrum disorders | Israel | *CYP2D6 *2, *3, *4, *5, *6, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52* and duplication | RIS and 9-OH RIS levels | RIS ($p$=0.03)<br>9-OH RIS (NS)<br>Active moiety (NS)<br>RIS/9-OH-RIS ratio ($p$=0.02) | Youngster et al[71] |
| Cross-sectional study | 23 | Healthy subjects | Chinese | *CYP2D6 *4, *5, *14A* | RIS and 9-OH RIS levels | RIS ($p$<0.001)<br>9-OH RIS (NS)<br>Active moiety (NS)<br>RIS/9-OH-RIS ratio ($p$<0.001) | Xiang et al[58] |
| Cross-sectional study | 83 | First episode Schizophrenia spectrum disorder | Croatian | *CYP2D6*3,*4, *5, *6 alleles CYP2D6** and duplication | RIS and 9-OH RIS levels | RIS ($p$<0.001)<br>9-OH RIS ($p$=0.008)<br>Active moiety ($p$=0.01)<br>RIS/9-OH RIS ratio ($p$<0.001) | Jovanovic et al[57] |
| **2. CYP2D6 polymorphisms and the efficacy of risperidone treatment** | | | | | | | |
| Observational cohort study | 136 | Schizophrenia, Schizoaffective disorder | Japanese | *CYP2D6*1, *5, *10* alleles | PANSS<br>SAS | PANSS total (NS), PANSS-P (NS), PANSS-N (NS) | Kakihara et al[69] |
| Case report | 1 | Schizophrenia | NA | *CYP2D6 *3, *4, *5, *6* alleles and duplication | PANSS | NA | Bozina et al[59] |
| Observational cohort study | 83 | First episode Schizophrenia spectrum disorder | Croatian | *CYP2D6 *3, *4, *6* alleles | PANSS | PANSS (NS) | Jovanović et al[57] |
| Observational cohort study | 76 | Schizophrenia | Spanish | PMs (*4/*4), IMs (*1/*4, *2/*4, *4/*35, *41/*41, *4/*9, *4/*41, *2/*6, and *4/*10), EMs (*1/*1, *1/*2, *1/*41, *1/*35, *2/*2, *2/*10 and *2/*35), and UMs (*1XN/*1). | PANSS | PANSS-T ($p$ = 0.011)<br>PANSS-N ($p$ = 0.001)<br>PANSS-P | Almoguera et al[70] |
| Observational cohort study | 40 | Autism spectrum disorders | Israel | *CYP2D6 *2, *3, *4, *5, *6, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52* and duplication | Improvement in disruptive behaviors after starting the treatment, no change, worsening disruptive behaviors | NS | Youngster et al[71] |

**3. CYP2D6 polymorphisms and adverse drug reactions**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *3.1 Metabolic* | | | | | | | |
| Cohort study | 81 | Schizophrenia or bipolar disorder | Romanian | *CYP2D6*4* | BMI gain | BMI gain ($p$<0.001) | Nussbaum et al[75] |
| Cohort study | 45 | Autistic | Portuguese | *CYP2D6*3, *4, *5, *6* and duplication | Weight gain | Weight gain ($p$<0.002) | Correia et al[68] |
| Cohort study | 123 | Acutely exacerbated schizophrenia | Han Chinese | *CYP2D6*10* | Weight gain | Weight gain ($p$<0.05) | Lane et al[67] |
| *3.2 Prolactin* | | | | | | | |
| Cohort study | 45 | Autistic | Portuguese | *CYP2D6*3, *4, *5, *6* and gene duplication | Prolactin | Prolactin level (NS) | Correia et al[68] |
| Cross-sectional study | 47 | Autism spectrum disorders and disruptive behavior disorders | Dutch | *CYP2D6*1, *3, *4, *5, *6* and *gene* duplication | Prolactin | Prolactin level (NS) | Roke et al[80] |
| Observational cohort study | 40 | Autism spectrum disorders | Israel | *CYP2D6 *2, *3, *4, *5, *6, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52* and duplication | Prolactin | CYP2D6 PM increase prolactin level ($p$=0.08), UM (NS) | Youngster et al[71] |
| Cross-sectional study | 147 | Autism spectrum disorders | Thai | *CYP2D6*1, *4, *5, *10* and **41* | Hyperprolactinemia | Hyperprolactinemia (NS) | Sukasem et al[84] |
| 3.3 Extrapyramidal syndrome | | | | | | | |
| Randomized crossover studies | 70 | Healthy subjects | Caucasian Spanish | *CYP2D6*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *40, *41, *1xN, *2xN, *4xN, *10xN, *17xN, *35xN,* and **41xN* | Neurological ADRs | NS | Cabaleiro et al[88] |
| Randomized crossover studies | 71 | Healthy subjects | Spanish | *CYP2D6*1, *3, *4, *5, *6, *7* and **9* alleles | Observe ADRs | NS | Novalbos et al[39] |
| Case report | 1 | Schizophrenia | NA | *CYP2D6 *3, *4, *5, *6* alleles and duplication | Observe ADRs | NA | Bozina et al[59] |
| Observational cohort study | 24 | NA | South African | *CYP2D6*1/*1, *1/*17, *1/*2, *2/*106, *2/*2, *2/*43, *1/*29, *2/*41, *35/*41, *1/*4, *2/*4, *2/*6B, *4/*35, *5/*17, *5/*41, *5/10B, *4/*4* | AIMS, BAS, SAS | EPS (NS) | Dodgen. et al[89] |
| Observational cohort study | 136 | Schizophrenia, schizoaffective disorder | Japanese | *CYP2D6*1, *5, *10* alleles | PANSS<br>SAS | SAS (NS) | Kakihara et al[69] |

(*Continued*)

**Table 5** (*Continued*)

| Study design | Total participants (n) | Subjects | Ethnicity | Genotypes | Outcome | *p*-value | References |
|---|---|---|---|---|---|---|---|
| Observational cohort study | 150 | Bipolar disorders, depression, drug addiction, psychotic disorders, schizoaffective disorders | Caucasian, Asian, Arab, African | *CYP2D6* *3, *4, *5, *6 alleles and duplication | UKU side effect rating scale | NS | Vandenberghe et al[90] |
| Observational cohort study | 560 | Schizophrenic disorders, mood disorders | NA | *CYP2D6**2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *45, and duplication | Abnormal Involuntary Movement Scale, UKU | Tardive Dyskinesia (NS) | de Leon et al[91] |
| Observational cohort study | 540 | Schizophrenia, schizoaffective, disorder, bipolar disorders, major depressive disorder | NA | *CYP2D6**2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *45, and duplication | UKU | Moderate ADRs ($p<0.05$) | de Leon et al[74] |

**Abbreviations:** ADR, adverse drug reaction; BMI, body mass index; EPS, extrapyramidal adverse effect; NA, not available; NS, not significant; OH RIS, 9-hydroxyrisperidone; PANSS, Positive and Negative Syndrome Scale; PANSS-N, PANSS-Negative; PANSS-P, PANSS-Positive; PANSS-T, PANSS-Total; PM, poor metabolizer; RIS, risperidone; SAS, Simpson and Angus Scale; UM, ultra-rapid metabolizer; BAS, Barnes Akathisia Scale; UKU, Udvalg for Kliniske Undersogelser.

D2 receptor blockages in the anterior pituitary lead to the increasing prolactin secretion. It could be an indirect way to measure the pharmacodynamics of risperidone. Even though numerous steady-state studies have found that the plasma prolactin concentrations were significantly associated with plasma 9-hydroxyrisperidone concentrations but not with plasma risperidone concentrations,[60–63] the results are inconsistent.[64] Weight gain is one of the essential ADR of risperidone.[65] Weight gain brings about the patient's noncompliance regardless of symptomatic improvement.[66] Even though little is known about the association between weight gain and *CYP2D6* polymorphisms, Lane et al reported a significant association between weight gain and *CYP2D6*10* allele in risperidone-treated patients.[67] Recently, Correia et al found UM to be associated with a less weight gain while on therapy when compared to the EM phenotype.[68] However, the PM phenotype showed similar effect as compared to the EM phenotype.[68] In conclusion, metabolism of risperidone relies on the number of active *CYP2D6* alleles, and some effects might be more common in the group of PMs. The findings proposed that the determination of an accurate *CYP2D6* genotype-predicted phenotype is necessary in the clinical setting and individualization of drug therapy.

## Impact of *CYP2D6* genetic variation on the efficacy of risperidone treatment

*CYP2D6* variations have a major effect on the pharmacokinetics of risperidone. Thus, the genetic variation of this gene plays a role in the efficacy of risperidone treatment. Risperidone had been used in many psychiatric diseases. Several pharmacogenetic studies showed the effect of *CYP2D6* variation in the treatment outcomes. However, there are controversial results for *CYP2D6* and risperidone efficacy. Several out of date studies showed no correlation of *CYP2D6* variation with risperidone treatment outcome.

A study of 136 patients who were diagnosed with schizophrenia, schizoaffective disorder, delusional disorder, and brief psychotic disorder and treated with risperidone single regimen showed no association between CYP2D6 polymorphism and clinical improvement results. Clinical improvement was evaluated using Positive and Negative Syndrome Scale (PANSS). Patients were genotyped as *CYP2D6* *1/*1 (n=16), *1/*10 (n=14), and *10/*10 (n=9). There were no differences in the clinical improvement among *CYP2D6* genotype in this study. Moreover, there was no correlation between the active moiety plasma concentrations (risperidone and 9-hydroxyrisperidone) and the percentage improvement of

total PANSS-Positive or PANSS-Negative scores. This study mentions the plasma concentration of active moiety that might play a role only in the extrapyramidal adverse reaction.[69]

One case report of a woman with schizophrenia who was treated with risperidone and followed up for 1 year also showed no significant association of *CYP2D6* genotype and clinical outcome. The patient was genotyped as *CYP2D6 *4/*6* and classified as PM. The PANSS score showed stable remission of illness over the stated period. Thus, PM phenotype of *CYP2D6* in this patient does not have a significant effect in clinical symptoms.[59] Similarly, the improvement of symptoms in 83 schizophrenia patients was not related to variations in *CYP2D6* and risperidone concentration data. The *CYP2D6* genotype was determined as *3, *4, and *6 alleles, and then grouped to *CYP2D6 wt/wt*, *wt/mut*, and *mut/mut*. Patients showed significant improvements in positive and general symptoms, but not associated with genetic variations which were classified in this study.[57]

On the contrary, a recent study[70] indicated the significant association of *CYP2D6* polymorphism and risperidone clinical improvement. Changes in PANSS total (PANSS-T), negative (PANSS-N), and positive (PANSS-P) scales were measured in risperidone-treated schizophrenic patients. If the changes of PANSS score were >50%, the patients were grouped as responders. The number of patients responding with treatment was evaluated with *CYP2D6* genotype. Predicted phenotypes were classified as PMs (**4/*4*), IMs (**1/*4*, **2/*4*, **4/*35*, **41/*41*, **4/*9*, **4/*41*, **2/*6*, and **4/*10*), EMs (**1/*1*, **1/*2*, **1/*41*, **1/*35*, **2/*2*, **2/*10*, and **2/*35*), and UMs (*1XN/*1). *CYP2D6* PMs showed a statistically significant clinical improvement in PANSS-T compared with EMs (66.7% vs 8.1%, $p$=0.011). The sample size of this study was too small. However, the power was enough to find an association with PANSS-T improvement. This study investigated many *CYP2D6* alleles and grouped into different metabolizer phenotypes according to the AS, which decrease the misclassifications.[70]

The other observational cohort study of children with autistic disorder, pervasive developmental disorder not otherwise specified, or Asperger syndrome who were treated with risperidone for at least 3 months showed the association of *CYP2D6* polymorphism with clinical response. Patients who had any combination of the null alleles (**3*, **4*, **5*, **6*, **52*, or **4xn*) were classified as PM. Patients with one nonfunctional *CYP2D6* null allele (**3*, **4*, **5*, **6*, **52*, **4xn*) and one low activity *CYP2D6* allele (**9*, **10*, **29*, **41*) were grouped as IMs, patients with one or two functional copies of the *CYP2D6* gene were grouped as EMs. Clinical outcomes were determined by asking the parents to grade the child's clinical response to treatment as improvement in disruptive behaviors after starting the treatment, no change, or worsening disruptive behaviors. The result showed that two PM patients were responders but had ADRs. In contrast, two patients were *CYP2D6* UMs and nonresponders and had no ADRs. Risperidone or its metabolite plasma levels did not show the difference in responders and nonresponders, or when comparing patients with or without ADRs. However, the results did not show the statistically significant difference due to small sample size.[71]

Although previous studies found the significant difference of risperidone and 9-hydroxyrisperidone between *CYP2D6* PMs and IMs or EMs, the total active moiety did not change too much between each phenotype groups. Therefore, the efficacy of risperidone may not be altered by *CYP2D6* polymorphism. There is no clarified study to determine the significant effect of *CYP2D6* variations with risperidone-treated clinical outcomes. The novel technic to detect several *CYP2D6* gene variations should be used to limit the misclassification of *CYP2D6* genotype. Moreover, suitable guideline to predict the phenotype should be applied to determine the activity of this enzyme. The precise classification of *CYP2D6* genotype and prediction of phenotype might lead to accurate study results. Furthermore, large sample size will increase the power of analysis and show the clarified result. Other studies in CYP2D6 polymorphism on the efficacy of risperidone treatment were listed in Table 5.

## The consequence of CYP2D6 polymorphisms in risperidone-associated ADRs

### Metabolic

The exact mechanism of risperidone-related metabolic adverse effects is inconclusive. Not all the patients treated with risperidone had metabolic adverse effects. This high interindividual variability in the risk of metabolic adverse effects proposed that genetics might play an essential role in a person's susceptibility to metabolic adverse effects, making it a target for pharmacogenetics studies.

Pharmacokinetic gene variation may be associated with the metabolism and disposition of risperidone. An individual's genetic variations might have an impact on the metabolism and disposition including safety, tolerability, and efficacy of the risperidone. One of the most important genetic factors influencing risperidone pharmacokinetics is phase I metabolism mediated predominantly by *CYP2D6*.[72] Since the antipsychotic drugs were metabolized by CYP2D6 enzymes, individuals with the PM-predicted phenotype

might suffer from dose-dependent complications because of increased plasma levels and result in serious toxicity of antipsychotic drugs.[73] Moreover, the *CYP2D6* PM phenotype was stated to relate with risperidone side effects and result in discontinuation.[74] Weight gain is one of the most important ADRs of risperidone.[65] Weight gain causes reduced patient compliance irrespective of symptomatic improvement.[66] According to the *CYP2D6* genotype, Nussbaum et al noted that the patients with **1/*4* genotype (IM phenotype) had significantly higher weight gain values than the patients who did not carry allele **4*, study in child and adolescent being on treatment with antipsychotics (risperidone, aripiprazole, or olanzapine).[75] Vicki et al reported that the patient treated with AAP which was *CYP2D6 *1/*3* or **4* genotype undergoing a larger percent body mass index change significant ($p<0.0097$) than those with a **1/*1* genotype.[76] Lane et al found a significant association between the *CYP2D6*10* allele and weight gain in patients with risperidone treatment.[67] The findings propose that this might be due to high concentrations of risperidone resulting in increased exposure, which may trigger risperidone-induced weight gain and metabolic effect. The *CYP2D6* genotype in children and adolescents might be a good predictor for the response to risperidone, and the side effects could be registered. Therefore, screening of pharmacogenetics is necessary in future clinical practice, allowing for personalized treatment, especially for at-risk individuals such asmetabolic.

## Prolactin

Elevation of serum prolactin is an indicator of dopamine receptor blockade at the level of the anterior pituitary lactotroph cells in the tuberoinfundibular pathway of the brain. A reduction in dopaminergic signaling pathway to the lactotroph cells results in a rapid increase in prolactin secretion. Such a reduction in dopamine can occur through the administration of antipsychotics. Among all AAPs, risperidone was reported to have high prevalence of hyperprolactinemia.[77] Several pediatric population studies in patients who were treated with risperidone account for 45%–70% of high incidence of hyperprolactinemia.[78–82]

Variation in the highly polymorphic *CYP2D6* was associated with risperidone-increased prolactin. A previous study has discovered the association between prolactin concentrations and *CYP2D6* polymorphisms of autism children receiving risperidone. An observational study of long-term risperidone evaluated prolactin response modified by *CYP2D6* among 47 children and adolescents aged 10–19 years with autism spectrum disorders or disruptive behavior disorders.[80] This study described that the number of patients with hyperprolactinemia was 100% (2/2) for *CYP2D6* PM, 47% (8/17) for *CYP2D6* IM, 48% (12/25) for *CYP2D6* EM, and no one (0/2) in CYP2D6 UM. A possible hypothesis may explain the interactions of 5-methoxytryptamine (5MT), *CYP2D6*, serotonin, and dopamine systems in relation to prolactin release from the pituitary.[83] With the properties of *CYP2D6* PM, deficient metabolized function may potentially display diminished serotonin reproduction from 5MT. As a result, this can lead to a higher dopamine tone in the anterior pituitary because serotonin generally exerts a tonic inhibitory effect on dopamine pathways. Consequently, after treatment with dopamine antagonist such as risperidone or perphenazine, a prolactin response could be noticed in *CYP2D6* PM.

However, the effects of the *CYP2D6* genetic polymorphisms on serum prolactin concentration are still controversial. This may relate to differences in methodology (e.g., retrospective and prospective open-label studies as well as case–control studies) or small sample size.[68,71] There is also a possibility for ethnic differences in genetic polymorphisms of *CYP2D6*. The *CYP2D6* PM phenotype in Asians is less frequent than that in Caucasians (e.g., ~1% in Thai, Chinese, and Japanese populations versus 5%–10% in Caucasians).[84,85]

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group[86] suggested that prolactin monitoring is recommended after 3 months of risperidone or other antipsychotics treatment and, if normal, on a yearly basis thereafter in asymptomatic children. The strongest predictors of hyperprolactinemia are the type and dose of the antipsychotic prescribed, such as risperidone, with increased levels observed at higher doses[81] along with plasma concentrations of 9-hydroxyrisperidone.[63] Although most of the studies have not exhibited an association between prolactin levels and adverse effects such as amenorrhea, galactorrhea, or gynecomastia, prolactin-associated adverse effects can occur with levels between 50 and 100 ng/mL.[87] Moreover, if amenorrhea has lasted for 12 months or longer in patients on antipsychotics, bone mineral density measurements should also be undertaken. Therefore, pharmacogenetic screening of hyperprolactinemia and regular monitoring of prolactin before and during treatment will help prevent those developing antipsychotic-induced hyperprolactinemia.

### Extrapyramidal syndrome

Neurological and extrapyramidal adverse effects (EPS) are the adverse effects of risperidone which were evaluated with *CYP2D6* polymorphism in several studies. However,

the impact of *CYP2D6* on EPS from risperidone is unclear. Although several studies showed no significant difference of EPS among *CYP2D6* variation, some of them showed a borderline significant trend. Two studies in healthy volunteers showed no association between *CYP2D6* polymorphism and adverse effects. The adverse effects of risperidone in 70 healthy volunteers were reported in this study. The most frequent adverse effects were neurological (somnolence (47.1%), headache (21.4%), and dizziness (17.1%)). In several genes, polymorphisms were associated with neurological adverse effects (*CYP2C9*, *NAT2*, *AGTR1*, *DRD2*, *CYP2C19*, and *CYP2C9*) and psychiatric effects (*CYP2C9* and *HTR2A*). However, there is no association between *CYP2D6* polymorphism and any adverse effects.[88] Other *CYP2D6* and risperidone studies on healthy volunteers also showed no significant difference of adverse effects among *CYP2D6*-predicted phenotype.[39] Even though the incidence of adverse effects was lower in the PMs (50%) than IMs (84%), EMs (73.5%), and UMs (83.3%), there is no significant difference. The similarity of risperidone and its active metabolite may cause the same adverse effect between each *CYP2D6* phenotype groups.[39]

One case report showed no adverse effects in schizophrenic patients who were treated with risperidone and showed no association with *CYP2D6* polymorphism. Although risperidone concentrations in this case were higher than normal, patients did not experience the toxicity of risperidone. The researchers hypothesized that the alternative metabolic pathway (*CYP3A*) might play a role in risperidone metabolism.[59] In a cohort study, 24 South African risperidone-treated patients presented movement disorders and weight gain adverse reactions from risperidone. The most common ADR is parkinsonism followed by dyskinesia. However, there is no statistically significant association between *CYP2D6* poor metabolism and risperidone ADRs.[89] Other studies[69] assessed extrapyramidal symptoms of patients using Simpson and Angus Scale (SAS) 2 weeks after the administration of risperidone. Even though the active moiety was positively correlated with SAS score, there were no differences in this score among *CYP2D6* genotypes. Because the active moiety was not different in each *CYP2D6* genotypes, *CYP2D6* polymorphism may not affect extrapyramidal symptoms in this study.[69] Similar to the previous study, there were no association of reported side effects (neurologic, cardiovascular, psychic, and sexual side effects) with *CYP2D6*-predicted phenotype. Only minimum active moiety concentration was found to be associated with neurologic symptoms, especially the severity of tremor.[90] However, one study showed a trend of the association between *CYP2D6* PM phenotype and the presence of tardive dyskinesia (TD). The result showed that a number of patients who had TD in *CYP2D6* PMs and non-PMs were 43% (16/38) and 31% (146/352), respectively. But, there was no significant difference between the two groups (odds ratio (OR) = 1.7, confidence interval (CI) = 0.84–3.2, $p$=0.14). Total risperidone duration was limited for PMs in this study. Only 79% (28/38) took risperidone for >6 months, and only 26% (10/38) for >1 year. Thus, even many patients who were exposed to risperidone for a very short duration developed TD.[91]

Little publication showed the association between risperidone-induced movement disorders and *CYP2D6* polymorphisms. The majority indicated no association, but some study showed a trend of correlation. One study showed the association of *CYP2D6* polymorphisms with EPS ADRs. There were 73 patients with moderate to severe ADRs in risperidone-taking group and 81 patients with ADRs who discontinued from risperidone group. EPS (resting tremor, stiffness, hypersalivation, and akathisia) was the most common ADR in both risperidone group (92%, 67/73) and discontinued from risperidone group (57%, 46/81). The other frequent ADRs were sedation and sexual problem. The *CYP2D6* PM phenotype was associated with risperidone ADRs in patients who take risperidone (OR = 3.4; CI = 1.5–8.0, $p$=0.004) and patients who discontinued from risperidone (OR = 6; CI = 1.4–25.4, $p$=0.02) after adjusting the confounding factor by multivariate analysis.[74] Although a significant association was found in this study, the small sample size of *CYP2D6* PMs was a concern. Many previous studies that found the association of CYP2D6 polymorphisms with risperidone ADR were shown in Table 5. Moreover, pharmacodynamic gene variations may play a greater role for risperidone ADRs. A further large prospective study should analyze both *CYP2D6* polymorphism and pharmacodynamic gene variations together to find the significant association.

## Challenges, opportunities, and future directions in the clinical application of genomic profiling in *CYP2D6*

From the previous study, *CYP2D6* phenotypes have been classified into 4 classes of enzyme activities according to the predicted phenotype model,[55,92] which can help to estimate the patient response. However, the IM phenotype consists of various genotype subgroups, and it might have an influence on the variation in *CYP2D6* enzyme activity within

this group. Stingl et al noted that *CYP2D6* IM phenotypes are carriers either of 1 normal allele + 1 nonfunctional allele (*1/def), 1 nonfunctional allele + 1 reduced-function allele (def/red), or 2 reduced function alleles (red/red).[93] Hendset et al reported that the def/red and red/red genotypes have 4.5-fold and 3.4-fold higher serum concentration of risperidone compared with *1/def genotype.[94] It means that there was a considerable variability in risperidone plasma concentration between *CYP2D6* intermediate genotype which carries 2 variant alleles or more than 1 variant allele. Moreover, Rau et al noted that patients with PM phenotype showed a 3-fold increased risk of ADR compare with EMs. Various enzyme activities are found in both the same phenotype subgroup and in the different phenotype subgroup.

According to the interindividual response, almost all the physicians adjust the daily dose of risperidone according to the clinical response of the patients. Therapeutic drug monitoring (TDM) is an important tool for therapeutic optimization, dosage assessment, and complementation in clinical treatment. Moreover, TDM can explain either the adverse effects or the responsiveness in patients treated with the drug that has a narrow therapeutic index or multiple medications. Therefore, TDM plays a crucial role in pharmacogenetic tests in order to optimize the dose of an individual patient.[95]

In natural setting, coprescription of drugs that belong to different classes is normal, especially in elderly patients. Patients who were treated with more multiple medication show more multidrug interactions. Generally, risperidone has been coprescribed not only with antidepressants and antiepileptics but also with other drugs in antipsychotics. The direct mechanistic evidence for the kinetics of drug–drug interaction in both 2-drug interaction and interactions of several drugs in combination has been studied.[96–98]

Mannheimer et al reported that the risperidone concomitance with CYP2D6 substrate drug did not have impact on the level of risperidone and 9-hydroxyrisperidone. It means that the risk of drug–drug interaction of CYP2D6 substrate is low in comedication. In addition, either a strong CYP2D6 inhibitors, bupropion, or a moderate CYP2D6 inhibitor, sertraline, will affect the serum concentration of risperidone, but no influence on 9-hydroxyrisperidone serum concentration.[99] The comedication of CYP2D6 inducer, rifampin, significantly decreased 51% of risperidone, 43% of 9-hydroxyrisperidone, and 45% of the active moieties of the mean area under curve.[100] In addition, the antiepileptic, carbamazepine decreases 50% of plasma concentration of both risperidone and its active metabolite.[101] As a result, the information regarding drug–drug interaction in CYP2D6 enzyme response may help in predicting and avoiding the clinical efficacy or toxicity.

There are several publications about the correlation among *CYP2D6* genotype, CYP2D6 enzyme activity, adverse events, and treatment outcome and risperidone therapy. This knowledge is very useful in terms of personalized medication. The dose recommendations of risperidone according to *CYP2D6* polymorphisms are an interesting study. A case–control study found that CYP2D6 PMs had a 3-fold increase in the risperidone ADR than EM patients.[102] The study published a case report of a patient with schizophrenia who was treated with risperidone for 1 year. She was identified as a CYP2D6 PM, and it was expected that she might have an accumulation of risperidone and influence on significant side effect. The plasma risperidone and 9-hydroxyrisperidone concentration were monitored, and the result showed the therapeutic index. Stable symptoms and no adverse effects were observed. Bozina et al suggested that CYP2D6 PM phenotype might not have an influence on the clinical significance of risperidone treatment because other pathways were metabolized risperidone.[59]

From the results of this research study, it is inferred that many factors influence risperidone metabolism. The challenge to use genetic-based treatment corresponds to many factors that affect the efficacy and toxicity. However, the questions as to what amount of dose should be adjusted for the dose regimens still remains. Steimer et al recommended the semiquantitative gene dose (SGD) system to apply genetic-based dose recommendation.[103] The amount of adjustment was calculated from the difference in mean concentration of each SGD group compared to the mean concentration of the total population. However, this study was performed in amitriptyline and the active metabolite.[104] Another strategy for dose adjustment is suggested by Kirchheiner et al who used the ratio of concentration in EM group as a reference group and that of other genotype groups to calculate the recommended dose for each individual group. Fifty percent dose reduction was recommended for PM of *CYP2D6* substrates.[105] Using a population pharmacokinetic approach is a strategy to find out a suitable risperidone dosage. Vandenberghe et al reported that *CYP2D6* but not *NR1/2*, *POR*, *PPARα*, *ABCB1*, *CYP3A* plays an important role in risperidone, 9-hydroxyrisperidone, and active moiety plasma concentration.[90] However, the CYP2D6 metabolizer subpopulation into PM, EM, IM, UM should be analyzed. From this result, it is found that *CYP2D6* is a major factor to provide a guideline for genotype-based dose recommendation.

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## Disclosure

The authors report no conflicts of interest in this work.

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