Pharmacogenomics for Psychiatry: Focusing on Drug Metabolizing Enzymes and Transporters, with Validated Methodology for *CYP2D6* and *CYP2C19* Including for a Novel Sub-Haplotype

by

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Abstract

Pharmacogenomics (PGx) is interested in the impact individual genetic makeup has on a patient's response to pharmacological agents. In clinical practice, PGx has the potential of reducing adverse drug reactions (ADRs), which cost Canada $65 million dollars in the year 2018, as well as enhancing treatment outcomes. Implementation of PGx in the clinic depends on, among other factors, a) knowledge of enzymes/transporters responsible for absorption, distribution, metabolism and excretion (ADME) and their genetic variation; b) the possible gene-drug pairs and drug interaction effects based on the genes that encode such enzymes/transporters; as well as c) robust methodology that can be applied in the genotyping efforts in order to generate individual data. The aim of my thesis is to address the aforementioned for advancement of PGx in psychiatric practice.

With these aims in mind, in the first part of Chapter 2, I review the main enzymes involved in phase I and II metabolism, as well as the transporters involved in phase III (excretion). The second part of the review presents pharmacogenetic associations important to psychiatry, that is, different examples of antipsychotics and antidepressants, as well as atomoxetine, are reviewed in relation to their metabolic pathway, introducing the gene-drug pairs that are of interest for devising pharmacogenetic guidelines. On this topic, existing guidelines by both the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) are also presented.

In Chapter 3, innovative methodology is introduced for the clinical genotyping of the genes *CYP2D6* and *CYP2C19* in a subset (N=95) of samples from the Genome-based therapeutic drugs for depression (GENDEP) clinical trial designed to investigate pharmacogenomic predictors of response to antidepressants. In it, the technologies used were: TaqMan copy

number variant (CNV) and single nucleotide variant (SNV) assays, xTAGv3 Luminex CYP2D6 and CYP2C19, PharmacoScan, the Ion AmpliSeq Pharmacogenomics Panel and the Agena MassARRAY. Through the employment of these different technologies, which were cross-validated, we were able to resolve samples that had been previously genotyped, but for which no data had resulted. This was enabled through the use of the above technologies and long-range polymerase chain reaction (L-PCR) with Sanger sequencing. An important contribution of the methodology described in the chapter is a validated methodology for a comprehensive range of *CYP2D6* haplotypes, including a larger range of hybrids and hybrid tandems compared to previous reports in the field.

Building on the work described above, Chapter 4 describes the genotyping of an individual sample that was initially detected from the genotyping work in Chapter 3. The sample of interest here was not concordant across the technologies used in terms of the genotypic automated call, which put into question the haplotypes present in the sample. Similar to Chapter 3, through the application of L-PCR and sequencing work, we were able to interrogate the SNVs present in the sample and, from the data generated, present a previously unreported sub-haplotype of *CYP2D6*41*.

Preface

This thesis is an original work by Beatriz Carvalho Henriques. The research projects described in Chapters 3 and 4, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board - Biomedical Panel. Project Name: "PRIME: Pharmacogenomics for the Prevention of Adverse Drug Reactions in Mental Health", No. Pro00069364, March 03, 2020.

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Chapter 3 of the thesis has been published under: Carvalho Henriques B., Buchner A., Hu X., Wang Y., Yavorskyy V., Wallace K., Dong R., Martens K., Carr M.S., Behroozi Asl B., Hague J., Sivapalan S., Maier W., Dernovsek M.Z., Henigsberg N., Hauser J., Souery D., Cattaneo A., Mors O., Rietschel M., Pfeffer G., Hume S., Aitchison K.J. Methodology for clinical genotyping of *CYP2D6* and *CYP2C19*. *Translational Psychiatry*, vol. 11, issue 1, 596. doi.org/10.1038/s41398-021-01717-9. I conducted experiments with TaqMan CNV for screening of samples as well as amplification of putative hybrids through L-PCR and sequencing work that followed, including some of my own primer designs for the sequencing work. Dr. Yabing Wang

in the Aitchison laboratory taught me how to do sequence alignment. As joint first authors, both Avery Buchner and I worked on edits and revisions of the paper to its final version.

Dedication

I would like to dedicate this thesis to my parents, Emilia and Francisco, and sister Helena for their unconditional support and love through this journey.

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The thesis presented here was made possible through the encouragement and support of a few individuals. First, I would like to acknowledge and thank Dr. Katherine J. Aitchison for her support and guidance throughout my graduate studies, for her encouragement for me to follow a career in research in the years before that and the countless teachings she has shared with me. It has been a privilege to be mentored by her and work in the dynamic and collaborative atmosphere she fosters in her research group.

Secondly, I owe many thanks to my colleagues in the lab who have accompanied me throughout this journey: Xiuying Hu, who was always willing to help and guide me if I had practical questions in the lab and who ensured the efficient functioning of our daily activities; Dr. Yabing Wang, who has helped guide me in my research and has shared his knowledge in different fronts; and Keanna Wallace, who has been a great support throughout the years.

Finally, I would also like to thank my supervisory committee members, Dr. Esther Fujiwara and Dr. Glen Baker, for their support and guidance through the different stages of my graduate work.

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List of Abbreviations and Acronyms

ADME - absorption, distribution, metabolism and excretion

ADR – adverse drug reaction

ASPE – allele specific primer extension

ATP – adenosine triphosphate

AUC – area under the curve

CNV – copy number variant

CPIC – Clinical Pharmacogenetics Implementation Consortium

CPZ – chlorpromazine

DDI – drug-drug interaction

DPWG – Dutch Pharmacogenetics Working Group

FMO – flavin-containing monooxygenase

GENDEP - Genome-based therapeutic drugs for depression

HAL – haloperidol

HET - heterozygous

IM – intermediate metabolizer

IVD – *in vitro* diagnostics

LAI – long acting injectable

L-PCR – long-range polymerase chain reaction

MALDI-TOF - matrix-assisted laser desorption/ionization-time of flight

MDD – major depressive disorder

MUT - mutant

NARI - noradrenaline reuptake inhibitor

NM – normal metabolizer

P-gp – P-glycoprotein

PGx - pharmacogenomics

PM – poor metabolizer

RIS - risperidone

SJS/TEN - Stevens-Johnson syndrome/toxic epidermal necrolysis

SNP – single nucleotide polymorphism

SNV – single nucleotide variant

SSRI – selective serotonin reuptake inhibitor

SNRI – serotonin norepinephrine reuptake inhibitor

TCA – tricyclic antidepressant

TDM – therapeutic drug monitoring

UM – ultrarapid metabolizer

WT – wild-type

CHAPTER 1: Introduction

Pharmacogenomics (PGx) may be defined as the study of how genomic variation affects response to pharmacologically active agents. An important tool in the advancement of precision medicine, PGx has the potential of improving patient care by tailoring medications so that possible side effects or adverse drug reactions can be minimized, as well as increasing the likelihood of efficacy in treatment, thus enhancing the quality of care one receives. While this is true for the medical sciences as a whole, as evidenced by the current number of gene-drug pairs with available prescribing guidelines in psychiatry (Bousman et al., 2021), the field of mental health and addictions has a lot to gain by the advancement of PGx. One important point is that such conditions have a significant impact on society both at the individual and economic level. In fact, a recent report found that for the period between 2010 and 2039, the global economy can expect to lose an estimated 16 trillion dollars due to mental illness (Patel et al., 2018). In addition, the remission rates seen in psychiatry are another reason why PGx has an important role to play in the field: it is estimated that only 33% (or 1 in 3) of patients with major depressive disorder (MDD), schizophrenia and bipolar disorder continue their medication owing to achievement of remission on treatment (Corponi et al., 2018). Moreover, it is estimated that hospitalizations alone owing to adverse drug reactions (ADRs) cost up to 65 million dollars to Canada (CIHI, 2019). Therefore, a tool that could assist with the prediction of response to a given treatment could be an important strategy to improve those remission rates as well as to decrease the incidence of ADRs.

Between 20 and 95 percent of the variability in the disposition and pharmacodynamics of drugs that act on the central nervous system (CNS) can be attributed to genetics. The range in the numbers is due to other factors, such as the environment, age, sex/gender and drug-drug interactions (Cacabelos et al., 2012). Nevertheless, the data are indicative of the importance of

individual genetic makeup in understanding response to drug treatment. Of particular relevance to PGx in psychiatry are the genes associated with drug metabolism and transport (Lapentina et al., 2020).

The genes that regulate drug metabolism and transport encode Phase I, Phase II and Phase III (elimination) reactions. The first are associated with either oxidation, reduction or hydrolysis reactions, while Phase II involve conjugation reactions. Phase III genes, on the other hand, are related to the transport of metabolites.

Within Phase I reactions, an important superfamily of enzymes – regulated by the genes of the same name – is the cytochrome P450 family. Between 60 to 80% of currently prescribed psychiatric drugs are metabolized by a CYP family enzyme, with particular emphasis given by the authors to CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6 and CYP3A4 (Cacabelos et al., 2011). Of these enzymes, the two most studied in the field of PGx in psychiatry are CYP2D6 and CYP2C19*,* which are the focus of Chapters 3 and 4. The genes that encode them are *CYP2D6* and *CYP2C19*, respectively.

CYP2D6 is the most studied drug-metabolizing gene in PGx and it is highly polymorphic due to characteristics such as high homology between the gene and the two pseudogenes *CYP2D7* and *CYP2D8*, that flank it (Bertilsson et al., 2002) and repetitive sequences between the genes in the *CYP2D* locus (Yasukochi et al., 2011). Currently, more than 140 haplotypes have been described for this gene, which illustrate its great variability. It was first described following the discovery that the hydroxylation of the anti-hypertensive debrisoquine was polymorphic (Eichelbaum et al., 1979). The frequency of the different known haplotypes of the gene varies by ancestral group. *CYP2C19*, while not as polymorphic as *CYP2D6,* still has significant variation, with the haplotypes **2*, **3* and **17* being the focus of the majority of studies to date on this gene.

To better classify the impact of haplotypes of these genes on metabolizer status, individuals are classified according to four different categories: poor metabolizers (PMs), where no functional allele is present; intermediate metabolizers (IMs), where reduced function of the gene is observed; normal metabolizer (NMs); and ultrarapid metabolizer (UMs), where increased activity of the functional gene is observed.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published extensive work including a particular focus on the role of the CYP2D6 and CYP2C19 enzymes in the metabolism of SSRIs (Hicks et al., 2015) and TCAs (Hicks et al., 2017), and the corresponding gene-drug pairs in prescribing guidelines. In addition, work is being progressing on the gene-drug relationship between *CYP2D6* and antipsychotics (guidelines are currently at a level B), while the Dutch Pharmacogenetics Working Group (DPWG) have well established guidelines (with clinical relevance at level A) for antipsychotics such as aripiprazole and olanzapine (Swen et al., 2011). The combined guidelines show the importance of these two enzymes for the field of psychiatry.

The work contained herein offers relevant contributions to the area of PGx in psychiatry, with particular focus on these two enzymes. Specifically, an overview of the contribution of the different phase I, II and III enzymes/transporters with particular focus on the CYP enzymes to PGx in psychiatry is given, as well as work conducted in the identification and characterization of *CYP2C19* and *CYP2D6*.

Firstly, in *How Can Drug Metabolism and Transporter Genetics Inform Psychotropic Prescribing?* (Chapter 2) I offer a review of the principal genes involved in the three metabolic phases described above, as well as of the genetic associations with neuropsychiatric drugs, where emphasis is given to the CYP family.

Secondly, in *Methodology for clinical genotyping of CYP2D6 and CYP2C19* (Chapter 3), the paper describes the validation of methodology for clinical genotyping of these two genes key to psychotropic prescribing in psychiatry. In doing so, we present consensus genotyping data resulting from different pharmacogenetics platforms, and confirmation of *CYP2C19* and *CYP2D6* haplotypes in 95 samples from Genome-based therapeutic drugs for depression (GENDEP), a large European study that investigated the difference in individual response to antidepressants. The work described here also offers revised genotypes for samples that had been previously genotyped using methodology with limitations (Huezo-Diaz et al., 2012).

Lastly, in *Identification of a Previously Unreported CYP2D6*41 Sub-Haplotype* (Chapter 4) I provide a follow up of the work conducted above where I describe the identification and genetic characterization of a novel sub-haplotype of the *CYP2D6*41* gene, also found in the GENDEP sample set.

CHAPTER 2: How Can Drug Metabolism and Transporter Genetics Inform Psychotropic Prescribing?

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2.1 Abstract

Many genetic variants in drug metabolizing enzymes and transporters have been shown to be relevant for treating psychiatric disorders. Associations are strong enough to feature on drug labels and for prescribing guidelines based on such data. A range of commercial tests are available; however, there is variability in included genetic variants, methodology, and interpretation. We herein provide relevant background for understanding clinical associations with specific variants, other factors that are relevant to consider when interpreting such data (such as age, gender, drug–drug interactions), and summarize the data relevant to clinical utility of pharmacogenetic testing in psychiatry and the available prescribing guidelines. We also highlight areas for future research focus in this field.

Keywords: pharmacogenomics (PGx), drug metabolism, drug transporters, cytochrome P450 enzymes, psychotropic drugs.

2.2 Introduction

Genome-wide association studies (GWAS) and related multi-omic strategies lend themselves well to phenotypes with polygenic modes of inheritance. By contrast, pharmacokinetic genes are associated with traits relevant to response to treatment (such as concentrations of medications and their metabolites) in an oligogenic manner with Mendelian patterns of inheritance and relatively large effect sizes. Many of the genes exhibiting a strength of association strong enough for consensus prescribing recommendations are in drug metabolizing enzymes (Hiemke et al., 2018). We herein provide a review of the genetics of drug metabolizing enzymes and transporters relevant for medications prescribed in psychiatry. We searched databases such as PubMed, PharmVar, PharmGKB, CPIC, DPWG, and DrugBank as well as relevant reviews, book chapters, and dissertations with search terms including each drug and drug metabolizing enzyme or transporter; each paper thus retrieved was reviewed by a minimum of two coauthors.

Drug metabolism and transport includes Phase I (addition of a reactive group to the molecule), Phase II (transfer of a polar group to the Phase I metabolite), and Phase III (transport of compounds away from the interior of the cells in an energy-dependent manner, introduced by Ishikawa (1992) (Xu et al., 2005). While the liver and gut are most relevant to phase I metabolism, the above activities occur throughout the body, with many drug metabolizing enzymes being widely expressed (Aitchison et al., 2010). Their activity is subject to mechanisms including competitive and non-competitive inhibition, and induction (Chen et al., 2018a; Chen et al., 2018b; Hisaka et al., 2010; Pelkonen et al., 2008).

2.3 Phase I Metabolism

Phase I enzymes catalyze reactions that alter the hydrophobicity, molecular weight, and reactivity of the substrate, occurring through hydrolysis, reduction, and oxidation reactions. Phase I enzymes relevant to psychotropics include the cytochrome P450 (CYP) family of

enzymes (Fig. 2.1), flavin-containing monooxygenases, esterases, epoxide hydrolases (EH), and microsomal epoxide hydrolases (mEH).

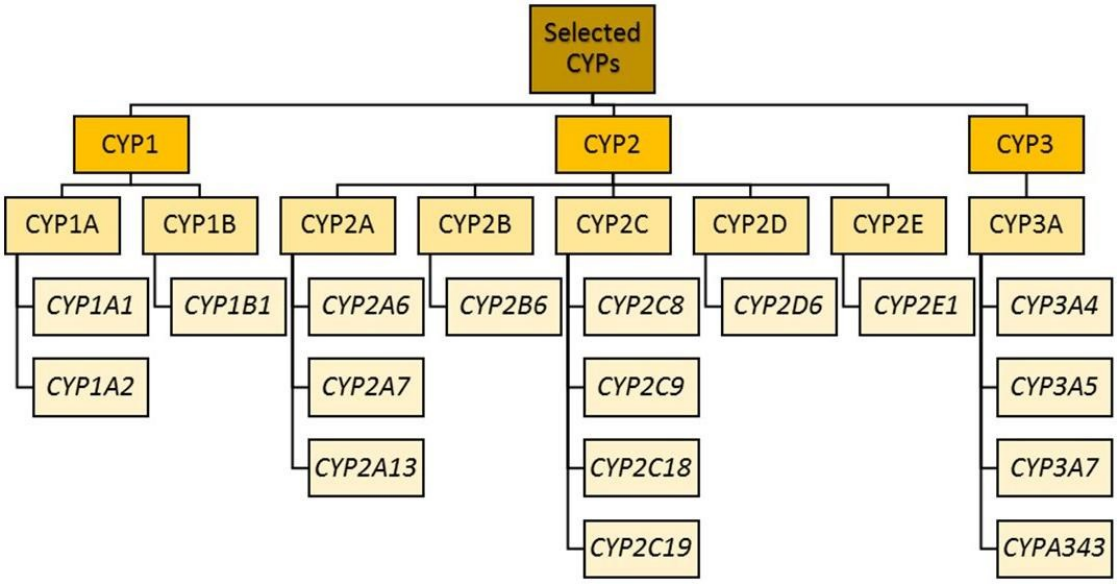

Figure 2.1 CYP enzyme families most relevant to psychotropic drug metabolism.

2.3.1 The Cytochrome P450 System

The CYP superfamily and flavin-containing monooxygenases (FMOs) are oxidoreductases. The most studied of these are the CYPs. Individuals sensitive to the antihypertensive agent debrisoquine and to the anti-arrhythmic agent sparteine gave rise to initial observations regarding variable enzyme activity (Eichelbaum, 1984; Johansson et al., 2011; Mahgoub et al., 1977; Smith, 1986). This led to sequencing efforts that identified the first *CYP2D6* loss-of-function mutation (Gough et al., 1990; Hanioka et al., 1990; Kagimoto et al., 1990). Multiple mutations in P450s relevant to psychotropics have since been discovered, with the frequency thereof differing by ethnicity (Aitchison et al., 2000c).

Cytochrome P450 enzyme classification (previously led by the Cytochrome P450 Nomenclature Committee and now transferred to the Pharmacogene Variation Consortium) is as

follows: after the letters “CYP” comes a number indicating the CYP family (Cupp et al., 1998). Enzymes within the same family (e.g., CYP1) have a minimum of 36% amino acid sequence homology. The next layer of differentiation is represented by a letter indicating the sub family. Within a subfamily (e.g., CYP1A), there is approximately 70% amino acid homology (Nebert et al., 1987). The final layer is another number representing the isoform (e.g., CYP1A1 and CYP1A2). For all, the enzymes are not italicized, while the corresponding gene names are.

Mutations in the CYP genes can be classified in two different manners: pharmacologically in terms of enzyme function, or genetically in terms such as loss or gain of function (van der Weide et al., 1999). Many CYPs have four distinct levels of enzyme activity: poor, intermediate, normal (previously known as extensive), and ultrarapid (Blake et al., 2013; Caudle et al., 2020). Reduced enzyme–substrate affinity, enzyme stability, or splice site variants leading to lack of functional protein can be a result of mutations. For reviews, see, for example, (Ingelman-Sundberg, 2004a, 2004b). Gene duplication (or multiple copies, i.e., multiplication) or single nucleotide variants (SNVs) affecting transcription, on the other hand, may be associated with increased enzyme activity (ultrarapid metabolizers; UM) (Johansson et al., 1993; Sim et al., 2006; Wang et al., 2015; Wang et al., 2014). Gain-of-function variants may increase medication clearance, consequently reducing the concentration, while loss-of-function mutations reduce clearance, increasing the concentration (Zanger et al., 2013); the opposite is true for prodrugs such as codeine, where loss-of-function mutations lead to lack of production of the pharmacologically active analgesic.

2.3.1.1 The CYP1 Family

The CYP1 family includes CYP1A and CYP1B. *CYP1A1* and *CYP1A2* lie in a head–head configuration on chromosome 15, and share a promoter region to which the aryl hydrocarbon receptor binds (at xenobiotic responsive elements) (Jorge-Nebert et al., 2010).

CYP1A2 Subfamily

Substrates specific to psychiatric conditions include antipsychotics [e.g., chlorpromazine (CPZ), trifluoperazine, clozapine, olanzapine], tertiary amine tricyclics (e.g., amitriptyline, imipramine, and clomipramine) as well as some selective serotonin reuptake inhibitors (such as fluvoxamine), and zopiclone. Additional substrates include analgesics (paracetamol), anti-inflammatories, cardiovascular agents (e.g., lignocaine), xanthines (caffeine, theophylline, aminophylline), and tacrine (Aitchison et al., 2000a; Imaoka et al., 1990; Lobo et al., 2008; Turpeinen et al., 2009; Zanger et al., 2013) . CYP1A2 is also involved in toxicity (e.g., bioactivation of arylamines and heterocyclic amines implicated in the formation of colon and bladder cancer, and the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, also known as MPTP) (Boobis et al., 1994; Coleman et al., 1996; Eaton et al., 1995; Hammons et al., 1997; McManus et al., 1990).

The enzyme is inducible by paracetamol, omeprazole, primaquine, carbamazepine, polycyclic aromatic hydrocarbons (e.g., 3-methylcholanthrene), heterocyclic aromatic hydrocarbons (such as 2,3,7,8-tetrachlorodibenzo-p-dioxin), and products of combustion such as cigarette or cannabis smoke (Aitchison et al., 2000c; Parker et al., 1998; Rost et al., 1994). Interestingly, a group of phenothiazines represented by perazine and promazine has been shown to induce this enzyme as well, accelerating their own metabolism and that of concomitant medications metabolized by this route (Wojcikowski et al., 2012). It can also be induced by various dietary substances including cruciferous vegetables (Cruciferae: including broccoli,

brussels sprouts, cabbage, cauliflower, radishes, and watercress), heterocyclic amines (produced in meat browned at high temperatures), and caffeine (Aitchison et al., 2000a; Aitchison et al., 2000c; Arici et al., 2017; Dobrinas et al., 2011; Ghotbi et al., 2007; Parker et al., 1998; Rost et al., 1994; Yoshinari et al., 2008). Amine metabolism may be affected by cruciferous vegetables for a significant duration (Murray et al., 2001), which may also affect other enzymes. The inducibility by smoking is of particular relevance to psychiatry, as many patients are smokers (Aitchison et al., 2000c; Dobrinas et al., 2011; Fiore et al., 1995; Ghotbi et al., 2007; Nakajima et al., 1999). Indeed, a recent study (Lesche et al., 2020) on the impact of genotype of various CYP enzymes (including CYP1A2) and the presence of known inducers and inhibitors demonstrated that, for patients prescribed clozapine, a greater percentage of the variation in plasma concentration of this medication was explained by smoking status than by *CYP1A2* genotyping information (in a cohort where 82% of individuals tested positive for the *CYP1A2*1F* variant).

Several polymorphisms have been detected in *CYP1A2* (Browning et al., 2010; Jiang et al., 2005). Individuals with the *CYP1A2*1F* c.−163C>A SNP that confers higher inducibility (Chida et al., 1999; Han et al., 2002; Sachse et al., 1998; Sim, 2013) have higher levels of caffeine metabolism. An initial report in Whites showed a reduction in olanzapine serum concentration in association with this variant (Laika et al., 2010). A subsequent study in Norwegian Whites was not able to replicate this association with olanzapine serum concentration, but in CSF the ratio of 4'-*N*-desmethylolanzapine to olanzapine was associated with smoking and *CYP1A2* genotype, with the highest ratios being in smokers homozygous for the *CYP1A2*1F* (Skogh et al., 2011). A later paper by the same group was also not able to replicate an association between the *CYP1A2*1F* and systemic exposure to olanzapine but did find a relatively modest effect of other variants - rs2472297C>T lying in the intergenic region

between *CYP1A1* and *CYP1A2* and rs4410790C>T upstream of the aryl hydrocarbon receptor locus (Soderberg et al., 2013). Attempts at replication of an association between the *CYP1A2∗1F* and olanzapine exposure in Asians have also been negative (Chen et al., 2005; Ghotbi et al., 2007; Nozawa et al., 2008; Obase et al., 2003; Shimoda et al., 2002).

There are also loss-of-function variants. The *CYP1A2*6* haplotype containing the c.1291 C>T (previously known as the c.5090 C>T) mutation causes an Arg431Trp amino acid substitution resulting in a complete loss of enzyme function (Chevalier et al., 2001; Zhou et al., 2004). By analogy, owing to the behavioral effects seen on administering clozapine to a *CYP1A2* knockout mouse, it is possible that people with this variant could experience more side effects of medications metabolized by CYP1A2, including clozapine and olanzapine (Aitchison et al., 2000b). The *CYP1A2*1C* haplotype has a promoter mutation (−3860 G>A) which has been associated with a reduction in caffeine metabolism in Japanese (Nakajima et al., 1999). Other known variants of *CYP1A2* with decreased activity include *CYP1A2*1K* (characterized by polymorphisms −729C>T, −739T>G, and −163C>A), identified in an Ethiopian population (Aklillu et al., 2003). Likewise, variants *CYP1A2*3* (2116 G>A and 5347 T>C) and *CYP1A2*4* (2499 A>T) are associated with reduced activity and have been identified (Chevalier et al., 2001; Zhou et al., 2004).[1] The *CYP1A2*7* has a splice site mutation in the donor site of intron 6 (3533G>A) and was found in heterozygous state in one patient with very high clozapine concentration and plasma caffeine clearance at the lower limit of the normal range, consistent with the mutation leading to no functional CYP1A2 enzyme (Allorge et al., 2003).

Many agents also contribute to the inhibition of CYP1A2, such as: apiaceous vegetables (parsnips, celery, dill, parsley) (Lampe et al., 2000), fluvoxamine (Brosen et al., 1993), grapefruit

[1] https://www.pharmvar.org/gene/CYP1A2

juice (Fuhr et al., 1993), estrogens (Abernethy et al., 1985; Knutti et al., 1981; Le Marchand et al., 1997; Rietveld et al., 1984; Vistisen et al., 1992), quinolone antibiotics (Fuhr et al., 1992), and in smokers, heavy ethanol consumption (Rizzo et al., 1997).

2.3.1.2 The CYP2 Family

CYP2 genes comprise clusters on different chromosomes (Sezutsu et al., 2013; Zanger et al., 2013).

CYP2A Subfamily

The CYP2A subfamily includes CYP2A6 and CYP2A13 (Hoffman et al., 2001; Zanger et al., 2013), with CYP2A6 being of relevance to psychiatry. CYP2A6 is mainly expressed in the liver, where it accounts for approximately 4% of total CYP content (Haberl et al., 2005; Shimada et al., 1994). CYP2A13 is expressed at reduced levels in the respiratory tract (Leclerc et al., 2011; Raunio et al., 2012). CYP2A6 was first recognized as the enzyme responsible for coumarin 7-hydroxylation, and is also the primary nicotine C-oxidase (Fuhr et al., 2007; Mwenifumbo et al., 2007; Pelkonen et al., 2000; Raunio et al., 2012). In addition to nicotine, CYP2A6 contributes to the metabolism of promazine, valproic acid, disulfiram, and caffeine as well as to other medications and toxins (Crespi et al., 1990; Gonzalez et al., 1994; Komatsu et al., 2000; Murai et al., 2009; Oscarson et al., 1998; Tanner et al., 2017b; Yamazaki et al., 1992).

Like many of the CYP superfamily, *CYP2A6* is a highly polymorphic gene, with many known mutations affecting enzymatic activity (Di et al., 2009; McDonagh et al., 2012). Polymorphisms arise from the occurrence of gene conversion events, deletions, duplications, multiple nucleotide insertions/deletions, and SNPs. The frequency of these events varies by ethnicity, with Asians having the highest frequency of loss-of-function mutations (~50%), and Whites the least (~9%) (di Iulio et al., 2009; Nakajima et al., 2006). *CYP2A6* expression and

activity are also impacted by induction and inhibition effects, age, and interactions with other hepatic enzymes, co-enzymes, and co-factors (Tanner et al., 2017b).

Loss-of-function is often a result of the common *CYP2A6*2* and *CYP2A6*4* alleles. With a frequency of 1–5% in Whites, the *CYP2A6*2* rs1801272 SNP encodes an inactive enzyme due to a Leu160His substitution (Tanner et al., 2017a). The *CYP2A6*4* haplotype (and its subtypes such as *CYP2A6*4A* and *CYP2A6*4H*) denotes a complete gene deletion, where the subtypes represent different genomic mechanisms for the deletion. This deletion is found at higher frequencies in Asians and Blacks e.g., *CYP2A6*4* has a haplotype frequency of up to 15% in a specific Asian group (Pang et al., 2015). Other variants such as *CYP2A6*9* result in a reduced enzyme functionality. Both complete loss-of-function and reduced function variants may result in a reduction of treatment efficacy, with atypical metabolite formation (e.g., switching from coumarin 7-hydroxylation to 3-hydroxylation) (Fujita et al., 2007; Hadidi et al., 1997; Komatsu et al., 2000). Associations between *CYP2A6* variants and smoking cessation have been reported (Tanner et al., 2017b).

CYP2B Subfamily

The CYP2B subfamily members are *CYP2B6* and a *CYP2B7P* (a pseudogene). CYP2B6 is strongly induced by phenobarbital (Faucette et al., 2004). It accounts for ∼1% of total hepatic CYP content (Ward et al., 2003), with variance in inter-individual expression of up to 300-fold (Desta et al., 2007; Hofmann et al., 2008; Lamba et al., 2003; Lang et al., 2001; Ohtsuki et al., 2012; Wang et al., 2008).

There are 38 different *CYP2B6* haplotypes currently described, some of which are associated with defined changes in enzyme function (Klein et al., 2005; Lamba et al., 2003; Lang et al., 2001; Lang et al., 2004; Zukunft et al., 2005). Two of the haplotypes are structural variants

representing hybrids whose sequence is partly derived from *CYP2B6* and partly from *CYP2B7P*, and gene duplications have also been identified (Martis et al., 2013). With a frequency of 15–50% across different ethnicities (of which Blacks have the highest), the most common allele is *CYP2B6*6*. The mutations c.516G>A and c.785A>G lead to amino acid substitutions Gln172His and Lys262Arg respectively, and are associated with a reduction in enzyme activity (Hofmann et al., 2008; Lang et al., 2001; Tsuchiya et al., 2004; Turpeinen et al., 2012). Those who contain homozygous copies of *CYP2B6*6* show increased plasma concentrations of relevant drugs, which has been linked to increased risk of Adverse Drug Reactions (ADRs) (Haas et al., 2004; King et al., 2008; Lubomirov et al., 2011; Ribaudo et al., 2006; Yimer et al., 2012; Zanger et al., 2007; Zanger et al., 2013). The *CYP2B6*4* has a haplotype frequency averaging at 9%, being up to 45% in Africans, 27% in Hispanics, 21% in Europeans, and 19% in Asians. The enzyme encoded by this variant clears bupropion [relevant for smoking cessation and also used in the treatment of depression and attention deficit hyperactivity disorder (ADHD)] more rapidly than the wild-type (Hesse et al., 2004; Kirchheiner et al., 2003; Lang et al., 2001; Rotger et al., 2007). The *CYP2B6*18* contains the c.983T>C substitution, which leads to Ile328Thr substitution. This haplotype is found in some African populations (e.g., the Bantu) (Jamshidi et al., 2010).

CYP2C Subfamily

Forming a ~390 kb cluster at chromosome 10q24, the CYP2C subfamily contains four genes: *CYP2C8, CYP2C9, CYP2C18*, and *CYP2C19* (Goldstein et al., 1994; Nelson et al., 2004). All exhibit extensive homology in both DNA and amino acid sequence, and are thus responsible for the metabolism of partially overlapping subsets of drugs (Coller et al., 2002; Koukouritaki et al., 2004; Lai et al., 2009; Naraharisetti et al., 2010; Ohtsuki et al., 2012; Rettie et al., 2005). Their main expression is in the liver, comprising 20% of hepatic CYP content (Shimada et al.,

1994). Within the CYP2C subfamily, *CYP2C9* is the most abundantly expressed, followed by *CYP2C8* and *CYP2C19*. Psychotropic substrates for CYP2C19 include diazepam (Jung et al., 1997), phenytoin (Bajpai et al., 1996; Mamiya et al., 1998), propranolol (Otton et al., 1990), selective serotonin reuptake inhibitors (Hicks et al., 2015), and tricyclics (Hicks et al., 2017). *CYP2C18* is distal to *CYP2C19* on chromosome 10 but appears to be expressed only at the mRNA level and not at the protein level (Chen et al., 2009).

CYP2C8 is the second most important cytochrome after CYP3A4 for the conversion of buprenorphine to its active metabolite, norbuprenorphine (Picard et al., 2005), and its expression is under genetic control. Work in Asian populations has identified variants that are associated with no functional enzyme, specifically the *CYP2C8*5.001*, the *CYP2C8*7.001*, and the *CYP2C8*11.001* at 0.006, 0.0025, and 0.003 (in Koreans; 0.01 in Vietnamese and 0.0014 in Chinese) frequency, respectively in E. Asian populations tested (Hichiya et al., 2005; Soyama et al., 2002; Yeo et al., 2011).

CYP2C9 metabolizes phenytoin. It is also relevant to drugs prescribed to treat physical comorbidities in those with chronic mental health conditions. These include anti-diabetic agents (such as tolbutamide, glimepiride, and nateglinide), angiotensin II blockers (losartan, valsartan, candesartan, and irbesartan), fluvastatin, warfarin, and nonsteroidal anti-inflammatory drugs including COX2 inhibitors (e.g., celecoxib) (Michaels et al., 2014). Of the reduced function variants, *CYP2C9∗2* and *CYP2C9∗3* are the most common, and have been studied in relation to the metabolism of drugs with a narrow therapeutic index, such as phenytoin, tolbutamide, and warfarin (Lee et al., 2002). The functional mutations in *CYP2C9*2* and *CYP2C9*3* are rs1799853 and rs1057910, leading to Arg144Cys and Ile259Leu substitutions. *CYP2C9*2* is associated with a 10-fold lower Vmax and 2-fold lower Vm for (S)-warfarin hydroxylation.

Median daily warfarin dose was in one study 4.0, 2.9, 2.6, and 1 mg for individuals of *CYP2C9*1/*1*, *CYP2C9*1/*2*, *CYP2C9*1/*3*, and CYP2C9 homozygous mutant genotype, respectively (King et al., 2004). Individuals who are affected by two reduced function alleles have a greater chance of ADRs such as gastrointestinal bleeding from NSAIDs (Martinez et al., 2004), hypoglycemia (Holstein et al., 2005), and bleeding from warfarin (Ogg et al., 1999). In a GWAS of response to warfarin, a *CYP2C9* marker was separately genotyped in addition to the array-based genomic analysis and was identified as the top signal (Takeuchi et al., 2009). Predictive modeling followed, and included a target of the drug (VKORC1), as well as CYP2C9 (Eriksson et al., 2012; Maagdenberg et al., 2018); the FDA label summarizes findings of a meta-analysis in which patients carrying at least one copy of the *CYP2C9*2* or *CYP2C9*3* alleles required a mean daily warfarin dose 17 or 37%, respectively less than wild-type individuals (Sanderson et al., 2005).

Like many CYPs (Kalow et al., 1992), CYP2C19 is also expressed extrahepatically in multiple tissues including in the brain (Aitchison et al., 2010). Substrates of this enzyme include: diazepam and its metabolite desmethyldiazepam, moclobemide (Roh et al., 1996), SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram), tertiary amine tricyclics (e.g., amitriptyline, imipramine, and clomipramine), as well as clozapine, olanzapine, phenytoin, and propranolol to lesser extents. The SSRIs fluoxetine and fluvoxamine also inhibit CYP2C19 (Preskorn, 1997). Conversely, phenothiazines represented by perazine and promazine have been shown to induce this CYP enzyme (Wojcikowski et al., 2012). Other substrates include the anticoagulant clopidogrel, cyclophosphamide, nelfinavir, proguanil, proton pump inhibitors omeprazole (Karam et al., 1996) and pantoprazole, thalidomide, and voriconazole (Desta et al.,

2002). Of the 35 allelic variants described in the CYP Database, *CYP2C19*2-*8* are the most common loss of function (poor metabolizer or PM) haplotypes.

There is substantial interethnic variation in the incidence of PMs of *CYP2C19*, being 2–5% in Whites, 2% in Saudi Arabians, 4% in Black Zimbabweans, 5% in Ethiopians, 13% in Koreans, 15–17% in Chinese, 21% in Indians, and 18–23% in Japanese (Aitchison et al., 2000c; Evans et al., 1995). When the square root of the PM phenotypic frequency (equal to the frequency of PM *CYP2C19* alleles) is plotted versus longitude, an increase in this value versus longitude may be seen, with an increment in the value occurring between Saudi Arabia and Bombay (Evans et al., 1995; Saeed et al., 2013). The increasing frequency of PMs is mainly owing to the higher frequencies of the null haplotypes *CYP2C19*2* and *CYP2C19*3*. The most common gain-of-function haplotype is the c.−806C>T (rs12248560) defining the *CYP2C19*17* haplotype. Of note, however, this may be found in combination with loss-of-function variants such as the c.1A>G (rs28399504) associated with the *CYP2C19*4* haplotype, or another loss of function variant (c.463G>T) (Scott et al., 2012; Scott et al., 2013; Skierka et al., 2014). It is therefore necessary to accurately characterize haplotypes with the c.−806C>T. Tables available via PharmGKB[2] provides further details on *CYP2C19* haplotype frequencies by ethnic group.

The most common PM haplotype is *CYP2C19*2*, which accounts for about 86% of all the PMs in the White population and 69–87% in the E. Asian population. The substitution of G681A in exon 5 of the *CYP2C19*2* haplotype creates an aberrant splice site (de Morais et al., 1994). The second most common PM haplotype is *CYP2C19*3*, which represents about 13–31% of E. Asian PMs and 1.5% of White PMs. The substitution of G636A mutation in exon 4 of the *CYP2C19*3* creates a premature stop codon. A third variant, *CYP2C19*4* accounts for

[2] https://www.pharmgkb.org/page/cyp2c19RefMaterials

approximately 3% of White PM alleles and contains an A → G mutation in the initiation codon (i.e., c. 1A>G). *CYP2C19*5* accounts for 1.5% of White PM alleles and is rare in East Asians. The *CYP2C19*5* haplotype is a result of a c.C1297T mutation in exon 9, in which causes an Arg433Trp change in the heme-binding region. *CYP2C19*6* (a c. G395A base substitution resulting in an Arg132Gln coding change in exon 3) and *CYP2C19*7* (a GT → GA mutation in the donor splice site of intron 5 at c.819 +2) each account for a further 1.5% of White PM alleles. *CYP2C19*8*, a T358C substitution in exon 3 that result in a Trp120Arg change, is a less common PM allele. The products of *CYP2C19*6* and *CYP2C19*8* show reduced catalytic activity (2% and 9% of wild-type S-mephenytoin hydroxylase activity, respectively); the others described above are associated with failure to express active *CYP2C19*. *CYP2C19*2A* and *CYP2C19*3* have both been identified in an Ethiopian population and found to account for all the PM alleles in the 114 individuals studied (Persson et al., 1996).

In *CYP2C19* PMs, diazepam clearance is significantly lower than in NMs (Bertilsson, 1995). The mean clearance is lower in Chinese compared to Whites. Owing to the relatively high frequency of PMs in East Asians, there is a greater frequency of individuals carrying one PM haplotype (i.e., heterozygous PMs). Consistent with this, it has been observed that physicians in Hong Kong prescribe smaller diazepam doses for individuals of Chinese ancestry compared to Whites (Kumana et al., 1987). The main variant responsible for this effect is the G681A, which has a gene-dosage association effect on diazepam clearance (Qin et al., 1999). For recent data on antidepressants and CYP2C19, see the relevant section (section 2.6.3 on this paper). Dose adjustment by *CYP2C19* genotype has been published for amitriptyline, citalopram, clomipramine, imipramine, moclobemide, and trimipramine (Kirchheiner et al., 2001). *CYP2C19*

PMs show a significantly higher efficacy for triple therapy for Helicobacter pylori (proton pump inhibitor, clarithromycin, and amoxicillin) (Klotz, 2006, 2009).

CYP2D Subfamily

The *CYP2D* subfamily consists of a gene cluster comprising *CYP2D6*, with two pseudogenes, *CYP2D7* and *CYP2D8* (Yasukochi et al., 2011). CYP2D6 accounts for 1.5% of microsomal CYP content in the liver (Michaels et al., 2014), and is involved in metabolizing the majority of psychotropic drugs (Bertilsson et al., 2002). It is also expressed in other organs, including the brain (Aitchison et al., 2010; Kalow et al., 1992; Niznik et al., 1990; Siegle et al., 2001), and has been associated with synthesis of neurotransmitters (Niwa et al., 2017; Yu et al., 2003). The *CYP2D6* gene is highly polymorphic, even compared to some of the other CYPs (Pharmacogene Variation Consortium: CYP2D6)[3]. It is the most extensively studied genetically variable drug metabolizing enzyme (Bertilsson et al., 2002) (Ingelman-Sundberg, 2004b), and has over 110 unique alleles identified (Kertesz et al., 2007).

These studies have revealed that there is significant variation of allelic variants between ethnic groups (Aitchison et al., 2000c)[4]. For example, the *CYP2D6*4* haplotype (previously known as g.1846G>A, genomic location of NG_008376.3 (Reference SNP (refSNP) Cluster Report: rs3892097)[5] 1847G>A, (Gough et al., 1990; Hanioka et al., 1990; Kagimoto et al., 1990) has a frequency of 19% in Whites (approximately 70–90% of all the PM alleles) (Aitchison et al., 1999), and 6% in Africans and 1% in South Asians (Aitchison et al., 2000c; Mammen et al., 2018). The second most frequent PM haplotype in Whites (2–2.5%) is *CYP2D6*5* (Aitchison et al., 1999), which represents a complete gene deletion, and occurs at a frequency of 5.3, 2.9, and

[3] https://www.pharmvar.org/gene/CYP2D6
[4] https://www.pharmgkb.org/page/cyp2d6RefMaterials
[5] https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs==3892097

2.9% in Africans, Asians, and Hispanics, respectively (Bradford, 2002; Del Tredici et al., 2018). The *CYP2D6*10* haplotype has key C188T and G4268C base substitutions in exons 1 and 9, respectively, that result in Pro34Ser and Ser486Thr amino acid substitutions (Sakuyama et al., 2008; Yokota et al., 1993). This haplotype is associated with reduced enzymatic activity (Johansson et al., 1994). With an allelic frequency of 0.43, it is very high in East Asians (Aitchison et al., 2000c; Mammen et al., 2018), and similar to other reduced activity metabolizers has been associated with ADRs such as tardive dyskinesia (Ohmori et al., 1998; Puangpetch et al., 2016). However, some of these apparent *CYP2D6*10* alleles may in fact be *CYP2D6*36* hybrid alleles. The *CYP2D6*17* haplotype exhibits a similar reduction in enzymatic activity (Masimirembwa et al., 1996; Oscarson et al., 1997), and is found predominantly in Africans, with frequencies of 34% in Zimbabwe, 28% in Ghana, 17% in Tanzania, and 9% in Ethiopia (Bertilsson et al., 2002). *CYP2D6*41* is the most common reduced activity (IM) haplotype in Whites, a key SNP 2989G>A (genomic position on NG_008376.3 7189G>A) occupying an intronic position leading to a splicing defect (Hicks et al., 2017; Hicks et al., 2013; Raimundo et al., 2000; Raimundo et al., 2004; Rau et al., 2006; Toscano et al., 2006; Wang et al., 2014). Tables available via PharmGKB[6] provide details of *CYP2D6* haplotype frequencies by ethnic group.

At the opposite end of the activity spectrum are the UM allelic variants, which most commonly have extra functional copies of the *CYP2D6* gene in tandem on the chromosome, seen at a frequency of 0.9–4% in Whites (Aitchison et al., 1999; Johansson et al., 1993). An apparently less common mechanism for UM alleles is upregulation of gene expression owing to SNP-related enhancer activity (Wang et al., 2015). Individuals possessing UM alleles were first

[6] https://www.pharmgkb.org/page/cyp2d6RefMaterials

identified as having lower than expected blood concentration of tricyclic antidepressants such as clomipramine (Bertilsson et al., 1993a; Bertilsson et al., 1993b; Dalen et al., 1998; Roberts et al., 2004). *CYP2D6* gene duplication or multiplication events occur at rates up to 29% in Ethiopians (Aklillu et al., 1996) by old techniques such as restriction fragment length polymorphism, and remain to be accurately characterized in terms of frequency using more current approaches.

The diversity in *CYP2D6* phenotype has clinical implications (Ingelman-Sundberg, 2005). Individuals with two PM haplotypes have no functional enzyme, are classified as PMs, and are more prone to ADRs for drugs with a narrow therapeutic window (Steimer et al., 2004, 2005). At the other end of the spectrum, UMs may also show more ADRs, such as tardive dyskinesia (Koola et al., 2014) or symptoms of morphine overdose on codeine (Crews et al., 2014), owing to enhanced formation of toxic metabolites (Pinto et al., 2011). Variation in *CYP2D6* is highly relevant to psychiatry: for most antidepressants and antipsychotics, there are clinical guidelines that state that pharmacogenomic information for *CYP2D6* could or should be used in prescribing (Bousman et al., 2019b). A review with modeling found that for antidepressants metabolized by CYP2D6, normal metabolizers (NMs) would require at least double the dose required by PMs, while cost analyses have associated PM status with not only higher ADRs but also with more drop outs from treatment (Chou et al., 2003; Kirchheiner et al., 2004; Tanner et al., 2020; Zhou et al., 2004).

Haplotype functionality may be used to derive an activity score (Caudle et al., 2020), with resources provided by PharmGKB to assist with this process. In the most recent update, the activity score of the *CYP2D6*10* haplotype was adjusted from 0.5 to 0.25, and the phenotype assignment for an activity score of 1 adjusted from NM to IM.

CYP2E Subfamily

A relatively small number of allelic variants have been identified for *CYP2E1*, such as *CYP2E1*2*, which is associated with reduced enzyme activity (Hu et al., 1997; Mittal et al., 2015). This enzyme is produced primarily in the liver, although it is also found in the brain (Garcia-Suastegui et al., 2017), and is responsible for metabolizing ethanol (into acetaldehyde), paracetamol/acetaminophen, and other substances into reactive intermediates, whose toxicity is enhanced in alcoholics (Cederbaum, 2012). Indeed, CYP2E1 is responsible for 20% of total ethanol metabolism (to which other enzymes such as catalases also contribute) (Heit et al., 2013). Gene transcription is induced by ethanol consumption [a moderate level of intake at 140 g ethanol per week producing an increase in expression of CYP2E1 in the intestine, but not in the liver; (Liangpunsakul et al., 2005)]. Interestingly, a 96-bp insertion polymorphism in the *CYP2E1* gene, which is associated with higher activity of the encoded enzyme, has been proposed as a possible protective factor against alcoholism (Cartmell et al., 2005). In addition to its relevance to alcohol use disorders, the role of CYP2E1 in metabolizing ethanol is a potential alcohol–drug interaction site. With occasional alcohol usage, medications such as clozapine at least partly metabolized by CYP2E1 may have their half-life increased owing to competitive inhibition with alcohol. With chronic alcohol use, the induction effect predominates, thus reducing the efficacy of CYP2E1-dependent drugs by decreasing half-life (Cederbaum, 2012).

In mice, tobacco smoke induces CYP2E1 activity in the lungs, liver and kidney (Zevin et al., 1999). In male smokers, CYP2E1 clearance may be increased (Benowitz et al., 1999). There may additionally be a complicated interaction effect of smoking and alcohol at CYP2E1, whereby CYP2E1 activity (as measured by chlorzoxazone metabolism) appears to be enhanced in non-alcoholic female smokers (Girre et al., 1994), while in males (Howard et al., 2003)

*CYP2E1 *1D* has been associated with nicotine and alcohol co-dependence in one study (Howard et al., 2003), which was not replicated in Taiwanese (Huang et al., 2018).

2.3.1.3 The CYP3 family

The CYP3 family comprises the CYP3A subfamily of four genes (*CYP3A4, CYP3A5, CYP3A7*, and *CYP3A43*) and two pseudogenes (*CYP3AP1* and *CYP3AP2*). CYP3A4 is the most abundant, although CYP3A4 and CYP3A5 have overlapping substrate specificity and in those deficient in CYP3A4, CYP3A5 and other members of the CYP3A family become crucial. The sum of the activity of all CYP3As is the total CYP3A activity, which is responsible for metabolizing ~50% of all clinically relevant drugs (Bu, 2006; Guengerich, 1999) as well as endogenous and exogenous steroids. They are found mainly in the liver, with lower concentrations found in the intestine, respiratory tract, brain, lung and kidney (Shimada et al., 1994). Owing to their intestinal and hepatic locations, these enzymes play a significant role in the first pass metabolism of all orally administered drugs. Similar substrate specificity is due to high sequence similarity between the enzymes. CYP3A can exhibit substantial interindividual and interethnic variation in its enzymatic activity or expression, partly owing to genetic polymorphism, marked effects of inducers and inhibitors, and epigenetic mechanisms of regulation of gene expression. CYP3A inducers (such as carbamazepine, phenytoin, rifampicin, and phenothiazines such as perazine and promazine) can greatly decrease plasma concentrations of other CYP3A substrates, resulting in reduced efficacy of the substrate (Gupta et al., 2018; Wojcikowski et al., 2012). Conversely, the administration of CYP3A inhibitors (e.g., ketoconazole) can increase the plasma concentration of other substrates, increasing ADRs or even toxicity.

Inhibition/induction effects at the level of the intestine may be more important than those occurring at the hepatic level for certain drugs in some individuals. Indeed, the effects of efflux

transporters such as p-glycoprotein can increase exposure of drugs to CYP3A enzymes in the intestine by prolonging transit time across the enterocyte (Wacher et al., 2001). Interestingly, there is broad overlap between substrates for and inhibitors of CYP3A enzymes and p-glycoprotein (Bruyere et al., 2010).

CYP3A4, is the most abundant CYP3A isoform in the intestine and liver (Nebert et al., 2002). Up to 30-fold interindividual variation in activity is seen (Ma et al., 2002); however, unlike the distribution of enzymes strongly under genetic control (such as CYP2D6), the distribution is unimodal. Some functional polymorphisms, such as *CYP3A4*22* (a intron 6 SNP, rs35599367, C>T), which is a loss of function mutation associated with 1.7–2.5 decrease in mRNA expression for heterozygous and homozygous carriers, respectively, have been identified in East Asians (who have a lower CYP3A activity) (Elens et al., 2011; Okubo et al., 2013; Wang et al., 2011). Two alleles associated with no active enzyme, *CYP3A4*20* and *CYP3A4*26*, have also been identified (Werk et al., 2014; Westlind-Johnsson et al., 2006). Recent screening of over 1000 Han Chinese for mutations in CYP3A4 found seven novel exonic variants (*CYP3A4*28-*34*) (Hu et al., 2017).

Midazolam clearance or an erythromycin breath test may be used in vivo to measure the activity of CYP3A enzyme in both the intestinal epithelium and liver (Goh et al., 2002). Alfentanil is demethylated by CYP3A4 and may be a useful CYP3A probe due to the pupillary response to alfentanil (Baririan et al., 2005; Klees et al., 2005). Other probes for in vivo CYP3A activity include: alprazolam (4-hydroxylation), cortisol (6-β hydroxylation), dextromethorphan (N-demethylation), diazepam (N-demethylation), nifedipine (oxidation), terfenadine (C-hydroxylation), testosterone (6-β hydroxylation), and triazolam (1-hydroxylation) (Jurica et al., 2012). Itraconazole and ketoconazole are potent CYP3A4 inhibitors (Jurica et al., 2012). Due to

the presence of multiple substrate binding domains within CYP3A4, the use of at least two structurally unrelated probe substrates is recommended when investigating inhibition effects; crystal structures show that multiple substrate/inhibitor molecules may be simultaneously bound (Ekroos et al., 2006; Foti et al., 2010; Korzekwa et al., 1998; Schrag et al., 2001; Tucker et al., 2001).

Although various functional genetic variants have been identified as above outlined, these do not account for the degree of phenotypic variation in enzyme activity seen at the population level. The major mechanisms for the regulation of *CYP3A* expression in fact appears to be epigenetic, including DNA methylation (Dannenberg et al., 2006), histone acetylation, and miRNA-mediated mechanisms. In the 5'-region of *CYP3A4* gene, histone acetylation occurs in response to the pregnane X receptor (PXR) agonist rifampicin (Xie et al., 2009). *CYP3A4* is also regulated in the promoter region of the constitutive androstane receptor (CAR) in response to dexamethasone at a lower rate of expression (Assenat et al., 2004). In addition, hepatocyte nuclear factor 4α can regulate the gene expression of PXR and CAR mediated xenobiotic induction of *CYP3A4* (Tirona et al., 2003). In regard to miRNA-mediated mechanisms, miR-27b regulates *CYP3A4* expression by binding to the 3'untranslated region (UTR) of *CYP3A4* mRNA (Pan et al., 2009), miR-148a regulates other liver specific genes by binding to the 3'UTR of PXR mRNA (Takagi et al., 2008), and the vitamin D receptor (VDR, also an indirect modulator of CYP3A) may be downregulated by miR-27b (Li et al., 2015). Target genes of the PXR are *CYP3A4*, *CYP2B6*, *MDR1*, members of UGT superfamily, multidrug resistance-related protein-3 (MRP3), and organic anion transporting polypeptide-2 (OARP-2) transporters (Klaassen et al., 2005; Tolson et al., 2010) in multiple cell types. P-glycoprotein expression at the blood brain barrier is regulated by PXR activation (Bauer et al., 2004). The PXR is also known as the steroid

and xenobiotic receptor (SXR); tamoxifen activates both *CYP3A4* and *MDR1* gene expression through the PXR/SXR in the breast cancer cells (Nagaoka et al., 2006). CAR, PXR, and VDR are members of the nuclear receptor family that also includes FXR, LXR, RXR, and PPARα, which together participate in the complex coordinated regulation of transcription of drug metabolizing enzyme and transporter genes (Czekaj, 2000; Czekaj et al., 2012). Genetic variants in nuclear receptors contribute to interindividual differences in response to drugs that are metabolized by CYP3A enzymes (Lamba et al., 2008).

The *CYP3A5*3* (6981A>G) and *CYP3A5*6* (14685G>A) splice site variants are associated with no functional protein (Kuehl et al., 2001) PharmVar CYP3A5 Page, retrieved from https://www.pharmvar.org/gene/CYP3A5). The *CYP3A5*7* variant (27126_27127insT) is also associated with CYP3A5 poor metabolizer status (Hustert et al., 2001).[7] The majority (80–85%) of White people are *CYP3A5*3/*3* genotype, which means they are *CYP3A5* poor metabolizers (van Schaik et al., 2002). Owing to this and other factors affecting *CYP3A* expression (see below), *CYP3A5* is expressed more frequently in those of African descent compared to Whites - 55% vs 33% in one study of 47 livers (Kuehl et al., 2001). However, as the lists of medications metabolized by CYP3A4 and by CYP3A5 overlap with each other and the sum of the activity in both of these enzymes is the total CYP3A activity, for many medications CYP3A4 is able to substitute for CYP3A5 in those who are *CYP3A5* poor metabolizers. For those who are *CYP3A5* extensive (normal) metabolizers, they require lower than the usual dose (of relevant medications such as tacrolimus) prescribed for Whites (Birdwell et al., 2015). Functional effects of combined CYP3A4 and CYP3A5 enzyme deficiency may be marked (Werk et al., 2014).

[7] https://www.pharmvar.org/gene/CYP3A5

Whilst CYP3A7 is mainly found in embryonic, fetal, and newborn liver, it may persist; it metabolizes dehydroepiandrosterone and its sulfate (DHEA-S). Persistent CYP3A7 expression in adults and lower levels of DHEA-S in women with polycystic ovary syndrome has been associated with a promoter variant, *CYP3A7*1C* (Goodarzi et al., 2008). Two pseudogenes are found between *CYP3A7* and *CYP3A5* [*CYP3A7-3AP1* and *CYP3A7-CYP3AP*; (Nelson et al., 2004); CYP3A5 RefSeqGene on chromosome 7, 2020, retrieved from https://www.ncbi.nlm.nih.gov/nuccore/NG_007938.2.

Of the total CYP3A hepatic content, CYP3A43 represents a relatively low proportion. Variants in this gene have nonetheless been identified and analyzed for association with clearance of antipsychotics (Variant Annotations). A frameshift mutation is present (c.74delA from the sequence start or c.-30delA from the ATG start, rs61469810), leading to a premature stop codon, a missense mutation (c.1018C>G/P340A, rs680055), and other silent/non-functional mutations. Increased olanzapine clearance in association with rs472660 AA genotype in the CATIE sample was found in an analysis of *CYP3A43* markers available on a particular array (the Affymetrix 500K) (Bigos et al., 2011). The A variant appears more frequent in those of African descent; after accounting for *CYP3A43* genotype, race was no longer a significant predictor of olanzapine clearance.

2.3.2 Flavin-Containing Monooxygenase

There are six human *FMOs* (Krueger et al., 2002), encoding enzymes FMO1-5 (the sixth gene is a pseudogene). FMO substrates include CPZ, trifluoperazine, prochlorperazine, promazine, promethazine, and other phenothiazines (Lomri et al., 1993), amphetamines, clomipramine, clozapine, desipramine, imipramine, ketoconazole, methamphetamine, moclobemide, olanzapine, ranitidine, and tamoxifen (Beedham, 1997; Foti et al., 2016; Motika et al., 2007).

FMO1 is expressed in adult kidney, intestine, and fetal liver (Yeung et al., 2000). Lower quantities are found in other organs such as the ovaries, testis, adrenal gland and bladder. Substrates include psychotropics mentioned above, disulfiram, nicotine, and pesticides (Phillips et al., 2017). Some of the variability in *FMO1* expression can be accounted for by a promoter SNP (characterizing the *FMO1∗6* allele), which has a frequency of 30, 13, and 11% in Hispanics, those of African descent, and Europeans, respectively.

2.3.2.1 Flavin-Containing Monooxygenase 2

Flavin-containing monooxygenase 2 (FMO2) is expressed in the lungs. The majority of Whites and Asians are homozygous for a non-functional allele: *FMO2∗2A* (a C>T mutation at position 1414 that results in a premature stop codon). The wild-type (*FMO2∗1*) haplotype is found in African-Americans (26%), Puerto Ricans (7%) and Mexicans (2%) (Furnes et al., 2003; Whetstine et al., 2000). In some populations in Africa, the frequency approaches 50% (Veeramah et al., 2008). The functional haplotype protects against toxicity caused by organophosphate insecticides, however, it also increases the risk of pulmonary toxicity for chemicals containing thioureas. It can metabolize drugs including nicotine, prochlorperazine, and trifluoperazine (Krueger et al., 2005) and is responsible for activating anti-tubercular drugs. Hormones including gonadal hormones (and possibly corticosteroids – a glucocorticoid responsive element has been found in the 5'flanking region of the rabbit *FMO2* gene) regulate FMO2 expression.

2.3.2.2 Flavin-Containing Monooxygenase 3

Flavin-containing monooxygenase 3 (FMO3) is present mainly in the liver; lower concentrations can be found in the lungs, kidneys, small intestine, and brain (Chen et al., 2016). Substrates include amphetamine, CPZ, clozapine, imipramine, methamphetamine, and nicotine.

Interindividual and interethnic protein concentration variability can be partially explained by the multiple SNPs that have been identified in the *FMO3* gene (Cashman et al., 2002; Krueger et al., 2002). These lead to amino acid substitutions or absence of functional protein, and are associated with the autosomal recessive hereditary condition of trimethylaminuria and milder forms thereof (Mackay et al., 2011). One such variant (Glu158Lys or E158K) may be associated with mild trimethylaminuria and potentially greater neurotoxicity of amphetamine and methamphetamine (which are metabolized to a greater extent to hydroxylamine metabolites by the E158K compared to the wild-type enzyme) (Motika et al., 2007). Trimethylaminuria may be associated with various neuropsychiatric presentations, ranging from depression, anxiety, suicidality, paranoia, addiction (Ayesh et al., 1993) to seizures (McConnell et al., 1997). Flavin-containing monooxygenase 3 converts trimethylamine to trimethylamine N-oxide, which is excreted in the urine, but also appears in the sweat, saliva, breath, and vaginal secretions.

Flavin-containing monooxygenase 3 activity is affected by hormones (the symptoms of trimethylaminuria can be worse in women, especially after puberty, after taking oral contraceptives, and at the time of the menstrual cycle or perimenopause), dietary content (choline, lecithin, tyramine), and intestinal bacterial overgrowth (reducing trimethylamine N-oxide to trimethylamine). Brussel sprout consumption acts as an inhibitor of FMO3, decreasing FMO3 activity, and can worsen the trimethylaminuria condition (Motika et al., 2007). For individuals deficient in FMO3, supplementation with folate and riboflavin is indicated (Motika et al., 2007). Choline and lecithin are found in egg yolk, kidney, liver, legumes, peas, salt-water fish, shellfish, and soybeans. The enzyme is subject to competitive inhibition effects (e.g., by CPZ, and imipramine) (Adali et al., 1998). Methimazole is a potent inhibitor of both FMO1 and FMO3. Recent publications have shown that N-oxidation of nicotine mediated by FMO1 and

FMO3 occurs in the brain, and, moreover, that functional variation in *FMO3* (rs2266780, E308G) is associated with nicotine dependence (Teitelbaum et al., 2018).

2.3.3 Esterases and Microsomal Epoxide Hydrolases

The metabolism of approximately 10% of therapeutic drugs with ester, amide, and thioester functional groups is catalyzed by esterases (Fukami et al., 2012). A common family of esterases, the B-esterase family, includes cholinesterases such as acetylcholinesterase (AChE). Cholinergic transmissions are regulated by AChE, selectively inactivating acetylcholine released from the presynaptic cleft of neurons of the brain, skeletal muscle, and the autonomic nervous system (Hasin et al., 2005).

Epoxide hydrolases are a family of enzymes that transform reactive epoxide molecules into more stable and more soluble diols (El-Sherbeni et al., 2014). *EPHX1* encodes mEH. It is a highly polymorphic gene, with over 100 SNPs identified. Enzyme activity is reduced by 40% in the variant with the c.337 T>C SNP, and 25% in the c.416 A>G variant (Caruso et al., 2014). Alcohol dependence has been associated with these SNPs (Bhaskar et al., 2013). Possibly altered response to carbamazepine and warfarin has been associated with genetic variants in *EPHX1* (Caruso et al., 2014; Daci et al., 2015; Liu et al., 2015; Nakajima et al., 2005; Puranik et al., 2013).

2.4 Phase II Metabolism

Phase II enzymes include glutathione S-transferases (GSTs), N-acetyltransferases, sulfotransferases, and UDP-glucuronosyltransferases (UGTs) (Jancova et al., 2010), the actions of which lead to the formation of more hydrophilic molecules for renal or biliary excretion (or further metabolite activation, which may be associated with toxicity).

Enzymes in this phase can be classified as either type I or type II conjugation. In type I, an activated conjugating agent combines with the substrate to yield a conjugated product through the addition of functional motifs (such as acetate, glutathione, glucuronate, or sulfate), consequently increasing the xenobiotic polarity and hydrophilicity. In type II conjugation, the substrate is activated and then combined with a moiety such as a methyl group or amino acid (Jancova et al., 2012).

2.4.1 Type I Conjugation

Cytosolic enzymes expressed in the liver and intestine are encoded by the genes *NAT1* and *NAT2*. *NAT1* shows additional wide tissue distribution (Sim et al., 2014; Sim et al., 2007; Windmill et al., 2000) and is expressed in fetal and neonatal tissue, while *NAT2* is not expressed until approximately a year later (Pacifici et al., 1986; Pariente-Khayat et al., 1991). The substrate specificity of NAT1 and NAT2 overlaps. Moreover, genetic variants in one are linked to those in another; they can therefore act in a concerted fashion to "cox and box" against evolutionary selection pressures with mutually compensatory mechanisms.

Glutathione S-transferases are relevant not only to drug metabolism, but also to detoxification of reactive intermediates such as those formed by catecholamine peroxidation (aminochrome, dopachrome, adrenochrome) in the defense against oxidative stress (Jancova et al., 2012). Glucuronosyltransferases are located mainly on the luminal membrane of the endoplasmic reticulum, and act in concert with the CYP enzymes present on the cytosolic surface (Ishii et al., 2007; Ouzzine et al., 1999). Some glucuronidated products are less active; others, such as morphine-6-glucuronide, are pharmacologically active (Gong et al., 1991). UDP-glucuronosyltransferase substrates of relevance to neuropsychiatry include: apomorphine, dopamine, ethanol, lamotrigine, morphine, oxazepam, serotonin, and valproic acid (de Leon,

2003; Ouzzine et al., 2014). In the brain, UGTs are found in the endothelial cells and astrocytes of the blood–brain barrier, as well as in the pituitary, pineal, neuro-olfactory tissue, and circumventricular organ (Ouzzine et al., 2014).

UDP-glucuronosyltransferase nomenclature is similar to that of the CYPs, with the UGT1 and UGT2 subfamilies being the most relevant for drug metabolism (Mackenzie et al., 2005).[8] UDP-glucuronosyltransferase activity is influenced by factors including cigarette smoking, obesity, age, and gender (Liston et al., 2001). Although relevant to the metabolism of both endogenous and exogenous substances, there are to date relatively few studies that have both therapeutic drug monitoring data and UGT enzyme phenotype (Stingl et al., 2014). UGT1A4, UGT1A6, and UGT2B7 are relevant to the clearance of multiple psychotropics including valproic acid, lamotrigine, olanzapine, clozapine, paliperidone, CPZ, and loxapine (Mazerska et al., 2016; Stingl et al., 2014). These enzymes are also expressed in the brain (Ghosh et al., 2013; King et al., 1999). Elevated plasma lamotrigine has been observed when given in combination with valproic acid, which has been attributed to competitive inhibition of UGT1A4 and UGT2B7 metabolism (Gidal et al., 2003; Rowland et al., 2006). Reduced lamotrigine clearance is seen in patients with benign unconjugated hyperbilirubinemia (Gilbert's syndrome), which is associated with the *UGT1A1∗28* haplotype in Whites and the *UGT1A1∗6* haplotype in Asians (Akaba et al., 1998; Barbarino et al., 2014; Beutler et al., 1998); UGT1A1 and common exons allele nomenclature[9]. Some associations as yet awaiting replication have been found: elevation of valproic acid clearance in carriers of *UGT1A3∗5* (Chu et al., 2012), reduction of lamotrigine clearance by 60% in those homozygous for *UGT2B7∗2* (Blanca Sánchez et al., 2010), and a doubling of the clearance in *UGT1A4∗3* heterozygotes (Gulcebi et al., 2011). A doubling in the

[8] https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/
[9] https://www.pharmacogenomics.pha.ulaval.ca/wp-content/uploads/2015/04/UGT1A1-allele-nomenclature.html

direct glucuronidation of olanzapine is seen in those of *UGT1A4∗3/∗3* genotype, with a reduction in those with at least one *UGT2B10∗2* variant (Erickson-Ridout et al., 2011). Individuals homozygous for the *UGT2B15∗2* haplotype have 50% lower benzodiazepine clearance (lorazepam, and the diazepam CYP metabolite oxazepam) (Chung et al., 2005; He et al., 2009). The 142T>G UGT1A4 polymorphism is associated with reduced clozapine and olanzapine concentrations (Ghotbi et al., 2010; Mori et al., 2005).

The human sulfotransferase superfamily of enzymes contains at least 13 members, with partially overlapping substrate specificity and tissue distributions (Riches et al., 2009). Some sulfo-conjugates are active; however, sulfo-conjugation usually reduces biological activity. For example, pregnenolone sulfate blocks the activation of GABAA receptors (Majewska et al., 1988), although it is a positive allosteric modulator of the NMDA receptor (Wu et al., 1991).

2.4.2 Type II Conjugation

Many exogenous and endogenous compounds can undergo N-, O-, S-, or arsenic-methylation (Feng et al., 2010). The co-factor required is S-adenosylmethionine (SAM), formed from ATP and L-methionine. Catechol O-methyltransferase (COMT) is a magnesium-dependent enzyme (Axelrod, 1957) that has a key role in the modulation of functions such as cardiovascular function, cognition, and pain processing, which are catechol dependent. Catechol O-methyltransferase is involved in the inactivation of catecholamine neurotransmitters (dopamine, noradrenaline), catechol-estrogens and other catechol drugs such as L–DOPA (Weinshilboum et al., 1999). There two forms of COMT: a cytoplasmic soluble form (S-COMT), and a membrane-bound form (MB-COMT), located on the cytosolic side of the endoplasmic reticulum. S-COMT is found in the liver, intestine and kidney (Taskinen et al., 2003), whereas the MB-COMT is more highly expressed in the central nervous system (Tunbridge et al., 2006). The *COMT*

Val158Met (rs4680) polymorphism has been associated with a variety of relevant phenotypes including cognition (Goldman et al., 2009), pain tolerance (Goldman, 2014), and age of onset of psychosis after adolescent cannabis consumption (Caspi et al., 2005; Lodhi et al., 2017).

2.5 Phase III Elimination

The final step in drug processing is the export of compounds away from the interior of cells in an energy-dependent manner. Metabolized molecules are transported by the ATP-binding cassette (ABC) superfamily (Hugo Gene Nomeclature Committee, 2020); energy (ATP) is used to transport substances out of the cell against a concentration gradient in multiple different organs including the brain during this phase (Borst et al., 2002; Dean et al., 2001; Doring et al., 2014).

ABCB1 (previously called *MDR1*) was the first member to be cloned (Riordan et al., 1985; Roninson et al., 1986; Ueda et al., 1987), with the encoded protein (p-glycoprotein or p-gp) being called multidrug resistance protein owing to the observation that it was overexpressed in tumor cells with resistance to multiple chemotherapeutic agents.

As reviewed elsewhere (Hodges et al., 2011), this protein has a complex structure. Two homologous halves each contain six transmembrane domains, which surround an aqueous pore within which conserved residues recognize a diverse range of substrates. It can distinguish stereoisomers and bind multiple substrates simultaneously in close proximity to each other, with associated allosteric, competitive and non-competitive inhibition, and cooperativity between substrates. Polymorphisms in *ABCB1* and their role in response to antidepressants have been reviewed (Hodges et al., 2011; Peters et al., 2009).

The most commonly studied variant is a triallelic SNP (c.3435T>C, c.3435T>G and c.3435T>A, reverse strand) (rs1045642). The c.3435T>C (or C3435T) is a synonymous SNP that is in linkage disequilibrium with another synonymous SNP (C1236T, rs1128503) and a

coding SNP (G2677T, (Database, 2020)). Haplotypes such as C1236T-G2677T-C3435T that include the C3435T have been associated with reduced inhibition by cyclosporin and verapamil of p-gp mediated substrate (in this case paclitaxel) efflux, with differences being more pronounced at higher levels of p-gp expression (Kimchi-Sarfaty et al., 2007). Sensitivity to rapamycin inhibition was not altered (Kimchi-Sarfaty et al., 2007). The altered sensitivity appeared to be owing to conformational change, as indicated by the use of a conformation sensitive monoclonal antibody (Kimchi-Sarfaty et al., 2007). The 3435C variant frequency varies between 34 and 90% in different ethnic groups ((Borst et al., 2002; Hodges et al., 2011).

P-gp substrates include many psychotropic drugs (e.g., fluvoxamine, paroxetine, venlafaxine, amitriptyline, desipramine, trimipramine, doxepin, olanzapine, risperidone (RIS), paliperidone, CPZ, diazepam, lamotrigine, carbamazepine, and phenytoin (Aller et al., 2009; de Klerk et al., 2013; Gunes et al., 2008; Lund et al., 2017; O'Brien et al., 2012; Palleria et al., 2013; Uhr et al., 2003; Uhr et al., 2008). Data on citalopram vary depending on the model system and fluoxetine and mirtazapine are not p-gp substrates (Peters et al., 2009). The list of non psychotropic substrates is extensive (Hodges et al., 2011).

Overlapping substrate specificity with other ABC transporters is present. P-gp is expressed on the apical membrane of the intestine from the duodenum to the rectum, being coregulated with CYP3A4 in the duodenum and jejunum, and coregulated with CYP3A5 in the rectum and sigmoid colon (Cascorbi, 2011; Ufer et al., 2008; von Richter et al., 2004). It shares substrate specificity with CYP3A4, and both are regulated by St John’s Wort (Johne et al., 1999), amongst other drugs. High affinity substrates such as verapamil also inhibit p-gp at the blood–brain barrier, causing drugs such as loperamide to affect the central nervous system (an anti-diarrheal medicine that normally has no central nervous system effects) (Elsinga et al.,

2004). A review on the topic of p-gp and its relevance to drug–drug interactions (DDI) underlines that data observed in vitro may not always be reflected by that seen in clinical practice in vivo (Lund et al., 2017). In vivo data indicate that carbamazepine and phenytoin are p-gp inducers, while fluvoxamine and paroxetine are p-gp inhibitors (Lund et al., 2017).

In the liver, p-gp levels vary 50-fold. More than 51000 mutations in the *ABCB1* gene region including over 137 missense[10] variants have been identified. Pharmacogenetic studies to date have often focused on a limited number of SNPs, such as the three described above. Data up to 2009 in regard to associations with response to antidepressants were summarized as equivocal (Peters et al., 2009), with a subsequent pharmacogenetically guided clinical trial (Singh, 2015) and a meta-analysis including this trial concluding in favor of this gene potentially having a role in pharmacogenetically guided treatment (Bousman et al., 2019a). There is suggestion that *ABCB1* should be considered together with *ABCC1* (Singh, 2015). (Amare et al., 2017; Fabbri et al., 2015; Lett et al., 2016) include data on *ABCB1* in their antidepressant response reviews, with a recent study in an E. Asian population reporting an association with response to serotonin noradrenaline reuptake inhibitors (SNRIs; (Shan et al., 2019)). In a review on clozapine, (Krivoy et al., 2016), concluded that *ABCB1* genotypes including the C3435T were associated with clozapine concentration and response.

While many studies have focused on the above outlined SNPs, particularly the C3435T, an approach in which haplotypes are linked to transporter phenotypes and systematically cataloged to inform clinical association analyses is surely desirable. For example, using in silico molecular techniques to predict amino acid residues that bind to psychotropics and hence which mutations might be investigated for clinical association analyses could be an informative

[10] https://www.ncbi.nlm.nih.gov/snp

approach. Further, elucidating mechanisms by which different co-administered medications might interact at p-gp would be helpful.

2.6 Pharmacogenetic Associations Relevant to Psychiatry

After initial prescription, psychiatric medicines have a 40–60% failure rate (Correll et al., 2015). Implementation of pharmacogenetics can improve current methods of physician judgment and therapeutic trials. Challenges to data standardization are prevalent (Altman et al., 2013; Bousman et al., 2018a; Bousman et al., 2016; de Leon, 2009; Malhotra et al., 2012). To address this, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was created in 2009 by PharmGKB and the Pharmacogenomics Research Network (Relling et al., 2011b) to provide prescribing guidelines for genetic variants. CPIC consists of four levels of recommendation concerning drug-gene pairs (Caudle et al., 2016).[11] Recommendation levels are denoted based on literature reviews presented to the CPIC writing committee. Evidence classifications include "high," "moderate," or "weak," based on design, quality, and generalizability of the research. Therapeutic recommendations are graded as "strong," "moderate," or "optional" (Caudle et al., 2014). Guidelines focus on gene–drug pairs where the prescribing recommendations are actionable (level A or B) (Table 2.1).[12]

[11] https://cpicpgx.org/prioritization/#cpicLevels
[12] https://cpicpgx.org/genes-drugs/

Table 2.1 Mental health medications: Clinical Pharmacogenetics Implementation Consortium (CPIC) evidence levels, pharmacogenomic FDA label, and associated genes.

Drug	CPIC level	PharmGKB level of evidence	PGx on FDA label	Gene
Amitriptyline	A	1A	Actionable PGx	*CYP2D6*
	A	1A	–	*CYP2C19*
Aripiprazole	B	3	Actionable PGx	*CYP2D6*
Atomoxetine	A	1A	Actionable PGx	*CYP2D6*
Brexpiprazole	B	–	Actionable PGx	*CYP2D6*
Carbamazepine	A	1A	Genetic testing required	*HLA-B*1502*
	A	1A	Actionable PGx	*HLA-A*3101*
Citalopram & Escitalopram	A	1A	Actionable PGx	*CYP2C19*
Clomipramine	B	1A	Actionable PGx	*CYP2D6*
	B	2A		*CYP2C19*
Desipramine	B	1A	Actionable PGx	*CYP2D6*
Doxepin	B	1A	Actionable PGx	*CYP2D6*
	B	3	Actionable PGx	*CYP2C19*
Fluvoxamine	A	1A	Actionable PGx	*CYP2D6*
Imipramine	B	1A	Actionable PGx	*CYP2D6*
	B	2A	–	*CYP2C19*
Nortriptyline	A	1A	Actionable PGx	*CYP2D6*
Paroxetine	A	1A	Informative PGx	*CYP2D6*
Perphenazine	B/C	–	Actionable PGx	*CYP2D6*
Pimozide	B	4	Genetic testing required	*CYP2D6*
Protriptyline	B	–	Actionable PGx	*CYP2D6*
Trimipramine	B	1A	Actionable PGx	*CYP2D6*
	B	2A	–	*CYP2C19*
Valproic acid	B	3	Genetic testing required	*POLG*
Venlafaxine	B	2A	Actionable PGx	*CYP2D6*

Prior to the implementation of CPIC, in 2005, the Royal Dutch Pharmacists Association established a similar body, the Dutch Pharmacogenetics Working Group (DPWG), to provide prescribing guidelines for specific gene–drug pairs to physicians and pharmacists in the Netherlands and now used internationally.[13] Similar to CPIC, evidence for strength of a prescribing recommendation (such as to avoid a particular drug in the presence of a specific genotype) is ranked on a 0–4 scale (Bank et al., 2018a). While there is significant overlap

[13] http://upgx.eu/guidelines/

between the recommendations offered by these two organizations, some differences in therapeutic recommendations can be found (Bank et al., 2018a; van Westrhenen et al., 2020).

Below are provided further details for pharmacogenetic associations for specific classes of medications relevant to psychiatry.

2.6.1 Mood Stabilizers

There is significant interindividual variation in treatment response and adverse reactions to mood stabilizers (Murru et al., 2015; Pisanu et al., 2016; Tang et al., 2015). The current CPIC gene–drug pair list includes carbamazepine, oxcarbazepine and valproic acid (Drozda et al., 2014; Saruwatari et al., 2010), with guidelines available for the first two (Phillips et al., 2018; Relling et al., 2011a).

Carbamazepine and oxcarbazepine are anticonvulsants approved for treating epilepsy, trigeminal neuralgia, and bipolar disorder (Phillips et al., 2018). Therapeutic drug monitoring for anticonvulsants is well-established. Both share dose-dependent (type A) ADRs including ataxia. Type B ADRs (not predictable from the pharmacology) are potentially lethal and include osteoporosis, aplastic anemia, and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Genetic variants having actionable levels with carbamazepine and oxcarbazepine are *HLA-B*15:02*, *HLA-A*31:01* and *SCN1A* (Phillips et al., 2018; Relling et al., 2011b). Associations have been shown in Asians with *HLA-A*31:01* and carbamazepine induced SJS/TEN (Ferrell et al., 2008; Stern et al., 2017). A 2004 report in Han Chinese found that the SJS/TEN frequency reduced to 0% after *HLA-B*15:02* genotype pre-screening (Chung et al., 2004). East Asians exhibit the highest *HLA-B*15:02* haplotype frequency (~15%) compared to other populations (>1%). In Hong Kong, Taiwan, and Thailand, testing for this haplotype prior

to prescribing carbamazepine and oxcarbazepine is standard practice (Chen et al., 2014; Lin et al., 2018; Sukasem et al., 2016a). However, recent data indicate that the *HLA-B*15:02* frequency in other populations may also be high enough to justify testing in other ethnic groups (Fang et al., 2019). *HLA-A*31:01* haplotype frequency also varies by ethnicity, being up to 15% in most Asian and White groups and infrequent in those of African descent (Fan et al., 2017).

Valproic acid (or its derivative, divalproex sodium, which is converted to valproic acid in the stomach) increases the levels of γ-aminobutyric acid (GABA) in the brain, blocking voltage gated ion channels (particularly calcium and sodium), and inhibiting histone deacetylase enzymes, including HDAC1. Genetic factors are associated with differential efficacy and ADRs (Fricke-Galindo et al., 2018; Kasperaviciute et al., 2009; Loscher et al., 2009). Hepatic metabolism occurs via CYP-mediated oxidation, glucuronidation, and mitochondrial oxidation (Chatzistefanidis et al., 2012; Ghodke-Puranik et al., 2013; Johannessen et al., 2010).

ADRs associated with valproic acid include hepatotoxicity, mitochondrial toxicity, and potentially fatal hyperammonemia encephalopathy, among others (Johannessen et al., 2010; Linnet et al., 1996; Singh et al., 2015). Valproic acid is contraindicated in patients with disorders secondary to mutations in DNA polymerase gamma (POLG), which replicates mitochondrial DNA. Patients with POLG-related disorders have elevated risk of fatal hyperammonemia encephalopathy. The onset of such may vary from childhood to late adulthood. It is therefore contraindicated in children with clinical suspicion of a hereditary mitochondrial disorder. In those over two years of age with suggestive symptoms (such as migraine with defined types of aura), valproate POLG testing is required[14], and it should be used if the testing is negative, other anticonvulsants have failed, and liver function is monitored.

[14] https://cpicpgx.org/genes-drugs/

2.6.2 Antipsychotics

In this section, pharmacogenetic data available for some specific medications are used to illustrate key applicable principles.

2.6.2.1 Perphenazine

Perphenazine undergoes substantial first-pass hepatic phase I and II metabolism. Serum concentrations vary widely due to polymorphisms in multiple phase I enzymes: up to 30-fold in *CYP2D6* NMs (Linnet et al., 1996). Initial studies showed that after 4–5 weeks, improvement was associated with plasma perphenazine concentrations above 2 nmol/l, while extrapyramidal effects occurred at concentrations above 3 nmol/l (Hansen, 1981; Hansen et al., 1983; Hansen et al., 1982). In a larger study of over 200 patients, a wider therapeutic range (2–6 nmol/l) was suggested (Hansen et al., 1985). Perphenazine binds dopamine D2 and alpha-1/alpha-2 receptors with 70 and 50% antagonism. The main active metabolite, 7-hydroxyperphenazine, binds dopamine D2 and alpha-1/alpha-2 receptors with 70 and 50% the antagonism of perphenazine (Hals et al., 1986). It is formed in a reaction catalyzed by CYP2D6, with other metabolites including *N*-dealkylated perphenazine (formed in part by other CYPs), and perphenazine sulfoxide (Dahl-Puustinen et al., 1989; Olesen et al., 2000). Compared to perphenazine, the concentration of perphenazine sulfoxide is in the same range, while *N*-dealkylated perphenazine is approximately three times that of perphenazine (Hansen et al., 1979). At therapeutically relevant concentrations of perphenazine, CYP3A4 accounts for about 40% of the *N*-dealkylation, with CYP isoforms 1A2, 2C19 and 2D6 contributing 20–25% (Olesen et al., 2000).

The peak serum concentration and the AUC of perphenazine for *CYP2D6* PMs is about 3 and 4 times, respectively that of NMs in single dose kinetics (Dahl-Puustinen et al., 1989), and at steady state, the median concentration-to-dose ratio of perphenazine in *CYP2D6* PMs is about twice that of NMs, with patients on concomitant inhibitors showing a median concentration in

between the two groups (Linnet et al., 1996). Researchers conducted a study of patients during treatment where *CYP2D6* genotype was shown to significantly predict the oral clearance of perphenazine (patients with two *CYP2D6* PM alleles having lower clearance than heterozygote PMs or NMs) (Jerling et al., 1996).

It would be expected that individuals deficient in CYP2D6 or on potent CYP2D6 inhibitors, higher perphenazine concentrations would be found and hence more adverse effects, whilst in *CYP2D6* UMs, there would be lower concentrations, with less adverse effects and potentially a lower therapeutic efficacy. Consistent with this, paroxetine, a potent CYP2D6 inhibitor (Lam et al., 2002), increases the AUC of perphenazine 7-fold in NMs, which is associated with increased side effects (Ozdemir et al., 1997).

2.6.2.2 Pimozide

Since 1984 pimozide has been used to treat Gilles de la Tourette's syndrome (Pringsheim et al., 2009), and also to treat psychotic disorders. Its use has been limited owing to an ADR of prolongation of the QT interval on the electrocardiogram, which is associated with risk for Torsades de Pointes (a type of ventricular fibrillation that may cause sudden cardiac death) (Agency, 1995; Fulop et al., 1987). In an isolated rabbit heart, this effect was shown to be attributable to pimozide itself, not to metabolites (Flockhart et al., 2000); this is due to an effect of the drug on potassium channels encoded by the human ether-a-go-go-related gene (HERG, otherwise known as KCNH2), which is responsible for the delayed repolarization current in the heart.

It is important to determine which CYP enzymes might contribute to the pimozide concentration profile. In vitro analyses showed that the formation of the major metabolite, 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one (DHPBI), by N-dealkylation was primarily

dependent on CYP3A4, with a lesser contribution by CYP1A2 (Desta et al., 1998). CYP2D6 may also play a role, but due to it being inhibited by pimozide, it was not possible to draw a conclusion regarding this from this in vitro study.

Case reports of interactions between pimozide and CYP2D6 inhibitors such as paroxetine and fluoxetine (Ahmed et al., 1993; Horrigan et al., 1994), as well as investigation of differential interaction with clarithromycin (an inhibitor of CYP3A) by CYP2D6 status led to recognition that CYP2D6 was a major contributor to the in vivo pharmacokinetics of pimozide (Desta et al., 1998). The effect of a single dose (6 mg) on the QTc interval (QT interval corrected for heart rate) was measured over time, and showed the greatest increase within the first 20 hours, with NMs showing a larger increase (by nearly 20 ms), followed by a reduction from 20 to 50 h, and then an increase at approximately 60–100 h. The late elevation was more significant in *CYP2D6* PMs, women, and clarithromycin-treated individuals, and appeared more sustained than the early increase. Owing to the more sustained nature, the late onset elevation may be more relevant to significant QTc prolongation; the early peak in NMs warrants further investigation in UMs. In *CYP2D6* PMs, half-life increased from 29 ± 18 h to 36 ± 19 h, while in NMs, the corresponding values were 17 ± 7 and 23 ± 10 h. For subjects with relevant data, the pimozide induced QTc interval changes coincided with the concentration-time course of pimozide. The prescription of CYP3A inhibitors, such as valproate, is now contraindicated with pimozide. In the above study, interestingly, pimozide rapidly increased plasma prolactin concentration, the maximum increase occurring 4 hours post dose, with a sharp reduction thereafter.

Simulated steady-state pharmacokinetic profiling of pimozide in *CYP2D6* PMs, IMs, and NMs led to specification in the FDA label in 2011 that *CYP2D6* PMs should not be prescribed more than 4 mg, with the maximum recommended dose in *CYP2D6* NMs being 10 mg (Rogers

et al., 2012). In the simulated data, 4 mg/day in *CYP2D6* PMs was the maximum dose that did not result in plasma concentrations in excess of those observed in *CYP2D6* NMs receiving 10 mg/day (Desta et al., 1998). Pimozide is commenced at 0.05 mg/kg (Preskorn, 2012), once daily. If the patient is a *CYP2D6* NM and is not on a CYP2D6 inhibitor, the dose may be increased every third day to a maximum of 0.2 mg/kg/day, to a maximum of 10 mg/day. If the *CYP2D6* status is not known, *CYP2D6* genotyping should be done before deciding to increase the dose above 0.05 mg/kg/d, which is the maximum dose for a *CYP2D6* PM, or if on a CYP2D6 inhibitor such as paroxetine, fluoxetine, and bupropion. Paroxetine will convert 60% of *CYP2D6* NMs to PMs at 20 mg daily, while at 40 mg daily, 95% will be phenocopied to PMs (Preskorn, 2003). Phenoconversion (the conversion of an individual's genetically defined metabolizer status to another status owing to the effect of a pharmacologically active substance) to *CYP2D6* PM status by the action of an enzyme inhibitor has been estimated as being 6 times more common than genetically determined *CYP2D6* PM status (Preskorn, 2012, 2013).

First pass metabolism of pimozide includes both the gut and the liver as CYP3A represents 70% and 30% of the total CYP450 in the intestine and the liver, respectively (Kolars et al., 1994; Shimada et al., 1994). Metabolism will be subject to the influence of gut microbiota, diet, and other factors including hormones (CYP3A4 being subject to regulation by the PXR and CAR) (Lamba et al., 2005; Pan et al., 2009). The drug label does not currently include dosing recommendations for *CYP2D6* UMs; further research including genotyping *CYP2D6* is required for pimozide, and other CYP2D6 metabolized medications.

It is suggested that *CYP3A4* also be genotyped for pimozide treatment, given its association with sudden cardiac death. It has a less clear genotype–phenotype relationship (with no updated data on PharmVar), and thus has not yet been introduced into clinical guidelines. In

the absence of genotyping, probe drugs such as nifedipine may be utilized to test the activity of multiple CYPs (de Andres et al., 2014); however, such estimation of CYP3A4 phenotype is influenced by any concomitant medication and/or dietary effects.

2.6.2.3 Haloperidol

Haloperidol (HAL) is a butyrophenone and first-generation antipsychotic (FGA) drug that acts as a dopaminergic antagonist in the mesolimbic system. It is used to treat a variety of psychiatric conditions, including psychoses (e.g., schizophrenia, schizoaffective disorder, bipolar disorder with mania or psychotic symptoms, substance-induced psychotic disorder) and other conditions with hallucinations (e.g., alcohol withdrawal, delirium, Lewy body dementia). Adverse effects may include tardive dyskinesia, neuroleptic malignant syndrome, and a prolonged QTc interval. Two major routes of metabolism, N-glucuronidation and O-glucuronidation, are affected by UGT enzymes, specifically the former by UGT1A4, and the latter by UGT1A4, UGT1A9, and UGT2B7 (Kato et al., 2012). Various CYP isoenzymes contribute to the metabolic pathways of this medication, most notably CYP3A4, and, to a lesser extent, CYP2D6. Cytosolic carbonyl reductase catalyzes the formation of reduced HAL, which retains 10–20% of the activity of the parent compound. Reduced HAL can be further metabolized by CYP3A4 to a tetrahydropyridine [Gorrod, 1993 #945]. The reduced drug can also be back-oxidized by CYP3A4 to HAL (Aitchison et al., 1999; Kudo et al., 1999; Pan et al., 1998; Tateishi et al., 2000). Owing to its lipophilicity, HAL is extensively metabolized in humans, with large interindividual variations in pharmacokinetics arising. With a proposed therapeutic range of 5.6–16.9 μg/l in serum (Ulrich et al., 1998), being able to appreciably predict pharmacokinetic parameters in individuals is of utmost importance to optimize efficacy and safety. At lower doses, CYP2D6 contributes to HAL metabolism significantly, but with higher doses, and longer term treatments, CYP3A4 back-

oxidation and N-dealkylation considerably outweigh the contributions of CYP2D6 (Fang et al., 1997; Pan et al., 1998; Zhou et al., 2009). Researchers showed that CYP2D6 PMs exhibited higher plasma concentrations of HAL over a 4-week treatment period with HAL decanoate, as compared to seven NMs in the study (Nyberg et al., 1995). However, another one showed that, in a large number of Japanese patients, the presence of neither an enzyme activity-reducing mutation (*CYP2D6∗10A*) nor activity-increasing mutations (duplications) in CYP2D6 alone could appreciably predict HAL concentrations (Ohnuma et al., 2003).

Haloperidol is a medication that is CPIC level B (for *CYP2D6*),[15] with a guideline currently in progress. Further, in the DPWG guidelines, there is a recommendation for initial dose to be reduced to 50% in PMs or for selection of an alternative medication based on a metabolic pathway different than CYP2D6. Possible dose adjustments are also mentioned for UMs.[16] In a study of 70 patients in which the most commonly prescribed medication was HAL, the risk of tardive dyskinesia increased with increasing number of functional *CYP2D6* genes, with UMs showing the highest risk (Koola et al., 2014).

Enzyme induction effects are also relevant for HAL metabolism. First, there is the effect of smoking. From a relevant review (Desai et al., 2001), it may be deduced that smoking increases the clearance of oral HAL (via effects including on CYP1A2), especially at doses lower than 0.5 mg/kg/day. Carbamazepine (which induces several CYPs including the CYP3As) reduces plasma HAL concentrations (Hesslinger et al., 1999).

[15] https://cpicpgx.org/prioritization-of-cpic-guidelines
[16] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-may-2020.pdf

2.6.2.4 Chlorpromazine

Chlorpromazine is a phenothiazine that was the first antipsychotic to be introduced (Basu et al., 2007). Its biotransformation includes hydroxylation (by CYP2D6 and CYP1A2), N-methylation, N-N-didemethylation, N-oxidation, S-oxidation, and glutathione conjugation. The hydroxylated metabolite can undergo further oxidation, leading to formation of an electrophilic quinone imine intermediate, which is capable of mediating toxic effects (by reacting with cellular proteins and DNA) or undergoing glutathione conjugation (Wen et al., 2009). Researchers confirmed the contribution of CYP2D6 to the hydroxylation pathway using quinidine, whilst also showing that *CYP2D6* genetic polymorphism was not the major contributor to inter-individual variability in plasma concentrations (Muralidharan et al., 1996). The latter finding was confirmed by Yoshii and colleagues (Yoshii et al., 2000), whose microsomal inhibition studies of CPZ 7-hydroxylation showed that CYP1A2 may play a more important role in the hydroxylation reaction for individuals deficient in CYP2D6. Indeed, Gill and colleagues reported that an individual with schizophrenia who was homozygous for the *CYP2D6*4* variant (then known as the "B") and therefore a PM and had been intolerant and non-compliant with multiple medications settled on a very low dose (50 mg) of CPZ (Gill et al., 1997).

2.6.2.5 Zuclopenthixol

Zuclopenthixol is a thioxanthene derivative used to treat schizophrenia, having high affinity for both D2 and D1 dopamine receptors (Kumar et al., 2005). Its metabolic pathways include sulfoxidation, *N*-dealkylation, and glucuronidation (Zhou et al., 2009), with metabolites not known to have antipsychotic activity.

A study (Dahl et al., 1991) showed that clearance of zuclopenthixol was associated with debrisoquine hydroxylation, and further studies confirmed the role of CYP2D6 in zuclopenthixol

metabolism (Zhou et al., 2009). Moreover, PMs had a 1.9-fold higher AUC of zuclopenthixol compared to NMs (n = 6 for each group) after a single 6 or 10 mg dose (Dahl et al., 1991). Similar results were found (Linnet et al., 1996): investigation of phenotypic relationships to zuclopenthixol concentration showed that, in 12 psychiatric patients, *CYP2D6* PMs had 60% greater concentrations than NMs, but were similar to NMs who were co-administered CYP2D6 inhibiting drugs.

Furthermore, in another study, psychiatric patients treated with zuclopenthixol who experienced adverse neurological events (tardive dyskinesia, parkinsonism) tended to have a higher frequency of non-functional *CYP2D6*3* and **4* alleles, but these results did not attain statistical significance (Jaanson et al., 2002).

Zuclopenthixol is CPIC level B,[17] with a guideline in progress (and also not yet available from DPWG). One review suggests considering dose adjustment (58 and 88% for *CYP2D6* PMs and IMs, respectively) or selecting an alternative medication (Stingl et al., 2013).

2.6.2.6. Aripiprazole

Aripiprazole was marketed as the first antipsychotic with dopamine and serotonin partial agonism. In Europe, aripiprazole is indicated for use in the treatment of schizophrenia and treatment of moderate to severe manic and episodes associated with bipolar I disorder and for the prevention of new manic episodes in those whose manic episodes respond to aripiprazole (Koskinen et al., 2010)[18,19]. Other licensed indications include adjunctive treatment of major depressive disorder, Tourette's syndrome, and irritability in autism spectrum disorder (Mailman

[17] https://cpicpgx.org/prioritization-of-cpic-guidelines
[18] https://www.medicines.org.uk/emc/product/7969/smpc
[19] https://www.ema.europa.eu/documents/product-information/abilify-epar-product-information_en.pdf

et al., 2010). Global therapeutic efficacy has been measured versus aripiprazole and dehydroaripiprazole serum concentrations, with a reported 68% response rate in those with concentrations of 150–300 ng/ml of aripiprazole, and a 57 and 50% response rate with concentrations less than 150 ng/ml or above 300 ng/ml, respectively (Kirschbaum et al., 2008). Therapeutic drug monitoring (TDM) has "recommended" (level 2 evidence) for aripiprazole by the interdisciplinary TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), with a therapeutic target range of 100–350 ng/ml for aripiprazole, or 150–500ng/ml for aripiprazole and dehydroaripiprazole (Hiemke et al., 2018).

Aripiprazole undergoes substantial first pass metabolism in the liver unless administered in a long-acting injectable (LAI) form. It is metabolized by dehydrogenation, hydroxylation, and *N*-dealkylation. In vitro studies show that CYP3A4 and CYP2D6 conduct the dehydrogenation and hydroxylation of aripiprazole, with CYP3A4 additionally catalyzing the *N*-dealkylation. Although a substrate for these enzymes, it does not appear to inhibit the activity of these enzymes. In clinical studies, 10–30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 or CYP3A4 activity as indexed by dextromethorphan; it does not appear to be an inhibitor of CYP2C9, CYP2C19, or CYP1A2 (Hjorthoj et al., 2015), nor a substrate for CYP1A enzymes, and hence no dose adjustment is required in smokers.

In a large pharmacokinetic study (N = 1288), *CYP2D6* PMs and IMs had a 1.4 times increase in exposure to the active moiety compared to NMs, leading to a 15% decrease in medication dosage of aripiprazole. Switch in medication from aripiprazole was not, however, significantly associated with *CYP2D6* status (Jukic et al., 2019).

The active dehydro-aripiprazole metabolite has a similar affinity as aripiprazole for dopamine D2 receptors; at steady state it represents about 40% of the plasma concentration of

aripiprazole (area under the curve or AUC; (Hjorthoj et al., 2015)), after oral administration or 29–33% after administration in the form of the LAI Abilify Maintena, and is therefore thought to contribute to the sustained pharmacologic effect of aripiprazole. Both aripiprazole and dehydro-aripiprazole are highly bound to plasma protein, mainly to albumin (DeLeon et al., 2004). The average elimination half-life is oral aripiprazole is ∼75 h, but in *CYP2D6* PMs, the average half-life extends to ∼146 h (Hjorthoj et al., 2015). The half-life of oral aripiprazole in *CYP2D6* IMs (75.2 h) was significantly longer than that in *CYP2D6* NMs (45.8 h); the systemic clearance of aripiprazole in IMs is approximately 60% that of NM subjects, with the maximum concentration being the same in IMs as in NMs (Kubo et al., 2007). At steady state, PMs have a significantly lower concentration to dose ratio than NMs, while in one report, IMs did not differ (van der Weide et al., 2015). However, the authors included in their IM group individuals who were heterozygous NMs (NM/PM genotype). In another report (Hendset et al., 2014), median serum concentrations were 1.6-fold or 1.8-fold higher in individuals of *CYP2D6* PM/IM or IM/IM genotype, respectively than in those who were heterozygous NMs.

For patients who are known *CYP2D6* PMs, FDA recommends administration of half of the usual dose of aripiprazole, and the DPWG guidelines recommend reducing maximum daily dose to 10 mg/day or 300 mg/month, i.e., 67–75% of the standard maximum dose.[20] Given that at a dose as low as 2 mg, D2 receptor occupancy is ∼70% (71.6 ± 5.5%, (Kegeles et al., 2008)) and the recommendation by consensus guidelines of doses of aripiprazole lower than those used in the initial marketing phase of the drug (Aitchison et al., 2009), it may well be recommendable to start at the lowest dose (2 mg) and to go no higher than 5 mg in *CYP2D6* poor metabolizers. While there are as yet no guidelines for other CYP2D6 phenotypic groups, in the case of IMs,

[20] https://www.knmp.nl/downloads/pharmacogenetic-recommendations-may-2020.pdf

the Japanese data would suggest that a cautious dosing in the 2–5 mg range should be appropriate.

In addition, packaging information for aripiprazole offers additional guidelines should the medication be taken with known CYP inducers or inhibitors (Abilify - aripiprazole tablet, 2016)[21]. In the case of co-prescription of CYP3A4 or CYP2D6 inhibitors, dosage is recommended to be reduced (by 50% in the case of strong inhibitors such as ketoconazole and fluoxetine, respectively). Likewise, should aripiprazole be taken with known CYP3A4 inducers, dosage increase is recommended (doubling in the case of carbamazepine). On cessation of any inhibitors/inducers, the dose should be readjusted accordingly.[22]

It has been noted that aripiprazole and 2,3-(dichlorophenyl) piperazine (2,3-DCPP), one of its metabolites, affect cholesterol biosynthesis by inhibiting 7-dehydrocholesterol reductase (DHCR7), the enzyme that converts 7-dehydrocholesterol (7-DHC) to cholesterol (Genaro-Mattos et al., 2018; Kim et al., 2016; Korade et al., 2016; Korade et al., 2010). Cholesterol is of critical importance to brain development; mutations in the *DHCR7* gene lead to Smith-Lemli-Opitz Syndrome, a neurodevelopmental condition, and exposure to DHCR7 inhibitors during the first trimester of pregnancy is associated with increased rates of fetal malformations, intrauterine death, and spontaneous abortions (Boland et al., 2016). Thus, aripiprazole should be contraindicated during the first trimester of pregnancy; the Summary of Product Characteristics states[23] that the above should indeed be avoided in pregnancy, unless the benefits expected from its prescription justify the posed risk to the fetus. The most critical period for formation of the neural tube is the first six weeks of gestation, when many women do not realize they are

[21] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac
[22] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=217e52b5-3a7b-4bbe-af3c-b18de7d426c3
[23] https://www.ema.europa.eu/documents/product-information/abilify-epar-product-information_en.pdf

pregnant. Therefore, it is recommended that women receiving aripiprazole in reproductive years should have a discussion of whether the woman is sexually active and of methods of contraception.

In a multiple-dose study, the mean terminal-phase elimination half-life of aripiprazole was 29.9 days and 46.5 days after 4-week injection of LAI 300 mg dose and 400 mg dose, respectively (Mallikaarjun et al., 2013). Data regarding differential half-life of the LAI by CYP2D6 genotype and/or CYP3A activity are not available. Aripiprazole lauroxil is a prodrug that undergoes bioactivation by hydroxylation and can be administered once every 6 weeks; it is similarly lacking pharmacogenetic data thus far (Frampton, 2017; Maini et al., 2021).

2.6.2.7 Risperidone

Risperidone is an atypical antipsychotic used for treating schizophrenia, acting mainly on 5-HT2A and D2 receptors (Zhou et al., 2009); it is converted to 9-hydroxyrisperidone (9-OH-RIS) by CYP2D6, with the latter being excreted in the urine and feces. In a meta-analysis (Stingl et al., 2015) suggested a dose adjustment of RIS to 56 and 146% in *CYP2D6* PMs and UMs, respectively, mentioning increased risk of toxicity in PMs. The DPWG note increased risk of treatment failure in *CYP2D6* PMs and UMs and recommend using 67% of the standard dose in the former and choosing an alternative drug or titrating the dose according to the maximum for the active metabolite (12 mg/day of paliperidone) in the latter. In a recent review (van Westrhenen et al., 2020), these recommendations were updated to suggest reducing the maximum dose by 33% (to 4 mg/day) in IMs as well as in PMs. For UMs, it was suggested to select an alternative medication or use therapeutic drug monitoring. It is worth noting that researchers have found significant differences in recommendations of RIS dosage according to

ethnicity (Cui et al., 2020). Specifically, adjustment in titration of this medication should be reduced in people of Asian ethnicity compared to Whites.

In a Norwegian population (Mannheimer et al., 2016; Mannheimer et al., 2014), it was found that the metabolic ratio (MR) for RIS, expressed as RIS/9-OH-RIS, was, not surprisingly, associated with *CYP2D6* PM status: an MR threshold of >1 predicted PM status with 91% accuracy (Mannheimer et al., 2016).

RIS metabolism by CYP2D6 is inhibited by the phenothiazine drug perazine when the two are co-administered (Paulzen et al., 2017), resulting in an increase in RIS and (RIS + 9-OH-RIS) concentrations and a reduction in the 9-OH-RIS/RIS ratio. Animal models have previously shown the role of phenothiazines in inhibiting the CYP2D family (Daniel et al., 2005).

In a study focusing on the relationship between genetic and epigenetic variation and response to RIS, three CpG sites in *CYP2D6* and two to three CpG sites in *CYP3A4* appeared to be more methylated in poor responders (Shi et al., 2017).

The effect of *CYP2D6* genotype on RIS metabolism has been studied in young Thai autistic spectrum individuals (Nuntamool et al., 2017). Genotypes *CYP2D6*5/*10, *10/*10* and **10/*41* showed reduced RIS metabolism, with significantly higher RIS plasma concentrations. While such an association was not seen in the *CYP2D6*4/*10* genotype group, this was likely owing to the relatively low frequency of the *CYP2D6*4* variant in this ethnicity, and the wide spread of the data in the small subgroup of *CYP2D6*4/*10* genotype. The *CYP2D6*10* variant was also associated with higher MR of RIS/9-OH-RIS. Researchers genotyped for *CYP2D6 *3, *4, *5, *6, *9, *10* and **41*, and classified as "*∗1/def*" (heterozygous for normal and deficient function) or "*def/red*" (heterozygous for deficient and reduced function); RIS serum concentration was 4.5 times higher in the *def/red* group compared to *∗1/def*. In addition, a 3 to 4-

fold increase in the serum concentration of RIS was shown in the *red/red* group (Hendset et al., 2014).

In addition to variation in metabolic activity and treatment response, Molden and colleagues found evidence of a relationship between genotype and discontinuation of treatment (Molden et al., 2016). Individuals classified as PMs for *CYP2D6* had active moiety (RIS + 9-OH-RIS) concentration 1.5 times higher than NMs. Consequently, there was an over-representation of adverse events and discontinuation of treatment for PMs. Conversely, a similar study with Croatian psychiatric patients receiving RIS injections found individuals classified as UM with concentrations of RIS active moiety (RIS + 9-OH-RIS) not reaching the threshold recommended for therapeutic range (Ganoci et al., 2016). An association was reported between the *CYP2D6*4* PM haplotype and treatment dropout due to poor response (Kaur et al., 2017).

In the largest study of RIS and *CYP2D6* to date (1288 patients), approximately 1.4 and 1.6-fold RIS exposure increase was observed in *CYP2D6* IMs and PMs, respectively (Jukic et al., 2019). A higher incidence of RIS-associated ADRs (de Leon et al., 2005) and treatment failure (Jukic et al., 2019) is observed in *CYP2D6* PMs compared with NMs, with increased treatment failure rate also being observed in *CYP2D6* UMs (Jukic et al., 2019). It is possible that the latter may be exposed to subtherapeutic drug concentrations, and also possible the effect of CYP2D6 on normally minor synthesis pathways for serotonin and dopamine may at least partly relate to such associations. Recent systematic reviews and meta-analyses support the need for dosage adjustment of RIS based on *CYP2D6* genotype (Cui et al., 2020; Zhang et al., 2020).

The relationship between *CYP2D6* and hyperprolactinemia (a possible adverse effect of RIS) appears to be U-shaped, with a tendency (though not consistently replicated) for both extremes of *CYP2D6* metabolic phenotype (i.e., PMs and UMs) to show an association with

hyperprolactinemia (Roke et al., 2013; Sukasem et al., 2016b; Troost et al., 2007; Youngster et al., 2014). Hyperprolactinemia has also been associated with the *DRD2 Taq1A* variant (Sukasem et al., 2018).

Interaction of known CYP2D6 inhibitors such as fluoxetine, bupropion, lamotrigine, sertraline, and citalopram are strongly correlated with the concentration of RIS in young male patients, compared to the available concentration of its metabolites (Calarge et al., 2011). A similar relationship has been described for thioridazine and levomepromazine (Mannheimer et al., 2008). The same relationship was not found for duloxetine, another known CYP2D6 inhibitor (Hendset et al., 2010). An association has been described between RIS discontinuation caused by DDI from CYP2D6 inhibitors (Ishak et al., 2008).

To a lesser extent, RIS metabolism is also mediated by CYP3A4 and DDI with inducers of this CYP enzyme are supported by the literature. Co-medication with armodafinil results in a decrease in plasma concentration of both RIS and 9OH-RIS (Darwish et al., 2015). The same relationship is true for rifampin (Kim et al., 2008; Mahatthanatrakul et al., 2007).

2.6.2.8 Olanzapine

Olanzapine is an antipsychotic licensed for use in schizophrenia and related psychotic disorders and bipolar disorder. The main circulating metabolites are desmethylolanzapine and olanzapine-10-glucuronide (Callaghan et al., 1999; Erickson-Ridout et al., 2011; Lu et al., 2016). The conversion to desmethylolanzapine is predominantly catalyzed by CYP1A2, with lesser roles for CYP2D6, CYP2C8, and CYP2C19 (Callaghan et al., 1999; Ereshefsky, 1996; Korprasertthaworn et al., 2015; Okubo et al., 2016). Okubo and colleagues investigated the role of CYP1A2, CYP2D6, and FMO3 in individuals of varying *CYP2D6* and *FMO3* genotype (Okubo et al., 2016). Olanzapine N-demethylation and N-oxygenation were found to be catalyzed by CYP1A2

and CYP2D6, and by CYP2D6 and FMO3, respectively, in experiments using liver microsomes and recombinant enzymes. The effects on olanzapine oxidation activities of furafylline (which inhibits CYP1A2), quinidine (inhibits CYP2D6), and heat treatment (inhibits FMO3-mediated activities) were investigated. Each, and the combination of all three treatments suppressed the metabolic clearances of olanzapine by 28, 33, 25, and 85%, respectively. Using recombinant CYP2D6 enzymes CYP2D6.1 and CYP2D6.10, only the wild-type variant was capable of the 2-hydroxylation conversion of olanzapine into 2-hydroxymethyl-olanzapine; CYP2D6 appears to be the only enzyme catalyzing olanzapine 2-hydroxylation. Direct glucuronidation (at the 10 and 4 positions) is conducted by UGT1A4 and UGT2B10, with the *UGT1A4∗3* and *UGT2B10∗2* haplotypes being associated with increased and decreased glucuronidation, respectively (Erickson-Ridout et al., 2011).

Drug-drug interactions (Flockhart)[24] are of importance in the prescription of olanzapine. CYP1A2 is induced by smoking; the plasma concentration to dose ratio of olanzapine is therefore lower in smokers (Tsuda et al., 2014). Inhibition of CYP1A2 by fluvoxamine also increases the concentration to dose ratio (Chiu et al., 2004). CYP1A2 is also inhibited by estrogens; as a result, gender (clearance is reduced in women) and body fat content influence the metabolism of olanzapine (Callaghan et al., 1999; Ereshefsky, 1996). Valproic acid co-prescription results in a decrease in olanzapine concentration (Vella et al., 2014). In contrast, protease inhibitors used in the treatment of HIV such as ritonavir in combination with fosamprenavir induce olanzapine metabolism (via CYP1A2 and/or UGT), leading to a recommendation to increase olanzapine dose by 50% when prescribed with such (Jacobs et al., 2014).

[24] https://go.drugbank.com/drugs/DB00334

2.6.2.9 Quetiapine

Quetiapine is another commonly prescribed antipsychotic. While literature supports CYP3A4 being the main enzyme in the quetiapine metabolic pathway, CYP2D6 is involved in the further metabolism of its principal metabolite, N-desalkylquetiapine. In an analysis of TDM data, patients from a Norwegian psychiatric hospital were genotyped for *CYP2D6*, *CYP3A5*, and *ABCB1* (3435C>T) and the associations with dose-corrected serum concentrations of quetiapine and N-desalkylquetiapine were analyzed (Bakken et al., 2015). The mean dose-corrected serum concentration (C/D) of N-desalkylquetiapine was estimated to be 33 and 22% higher in *CYP2D6* PMs (P = 0.03) and heterozygous *CYP2D6* NMs (P = 0.001), respectively, compared with *CYP2D6* NMs. There was no significant association with *ABCB1* 3435C>T polymorphism or *CYP3A5* genotype.

Quetiapine has, however, been observed to have a serum level 2.5 times higher in those either heterozygous or homozygous for *CYP3A4∗22* compared to those of *CYP3A4* wild-type (van der Weide et al., 2014), with concentration to dose ratios that were 67% higher. The percentage of patients who had levels of quetiapine above the therapeutic range was also about five times higher in the *∗22* carrier group (16.1 versus 2.9%). Quetiapine serum levels based on reduced CYP3A4 metabolic activity were comparable to results found with co-administered CYP3A4 inhibitors, such as ketoconazole. The frequency of the *CYP3A4∗22* haplotype is up to 10%.

In terms of DDI, valproate coadministration with quetiapine appears to result in a variable degree of increase in quetiapine plasma levels (Aichhorn et al., 2006; Winter et al., 2007), which may result in toxicity on occasion (Anderson et al., 2000). In a review of therapeutic monitoring data from more than 2000 patients, it was reported that the following factors were associated with an increase in quetiapine concentration: age of at least 70 years,

comedication with clozapine, fluvoxamine, and to a lesser extent citalopram/escitalopram, while, conversely, the following were associated with reduced quetiapine concentration: age under 18 years and comedication with carbamazepine or oxazepam, and to a lesser extent levomepromazine or lamotrigine (Castberg et al., 2007). The largest effect sizes were seen with fluvoxamine (+159%), clozapine (+82%), age at least 70 years (+67%), and carbamazepine (−86%). Another study found that dose-corrected quetiapine concentrations were approximately 60% lower in patients co-medicated with lamotrigine (Andersson et al., 2011).

2.6.2.10 Ziprasidone

Ziprasidone is a less commonly prescribed antipsychotic. Data indicate ziprasidone is mainly metabolized by glutathione and enzymatic reduction by aldehyde oxidase, followed by S-methylation to S-methyl-dihydroziprasidone by thiolmethyltransferase (Obach et al., 2005). Approximately one-third of its clearance is thought to be CYP3A4-dependent (Beedham et al., 2003). It is therefore subject to CYP3A-mediated induction (e.g., by carbamazepine, (Miceli et al., 2000)) and inhibition effects. As this medication has been associated with increases in the QTc interval (Aronow et al., 2018), inhibition effects (e.g., by fluvoxamine or ketoconazole) should be avoided. Ziprasidone is also contraindicated in the presence of other medications that also prolong QTc (Hicks et al., 2017; Kutcher et al., 2005).

2.6.3 Antidepressants

Tricyclic antidepressants (TCAs) and SSRIs both undergo first pass metabolism in the liver, with the CYP enzymes playing a prominent role in this. The cytochromes involved include CYP2D6, CYP2C19, CYP2C18, the CYP3A family, CYP1A2, CYP2C9, and CYP2B6, with the first two

enzymes having a higher affinity for most antidepressants than the rest of the enzymes (Brosen, 1993; Jann et al., 2000; Koyama et al., 1997).

2.6.3.1 Tricyclic Antidepressants

Imipramine, the first TCA was derived from a phenothiazine, showing improvement without serious side effects in 500 patients with severe depression (Hillhouse et al., 2015; Kuhn, 1958). Although TCAs are still used (e.g., second-line or with somatic symptoms) to treat depression (Kennedy et al., 2016; Uher et al., 2009a), the treatment of pain (e.g., migraine, neuropathic, cancer-associated) is now their more common therapeutic use (Baltenberger et al., 2015; Laird et al., 2008; Watson, 2000).

Tricyclics include tertiary and secondary amines. A tertiary amine has a nitrogen bonded to three carbons, while in the case of a secondary amine, the nitrogen is bonded to only two carbons. The tricyclics amitriptyline, clomipramine, imipramine, trimipramine, doxepin, and dothiepin are tertiary amines. Tertiary amines are demethylated to secondary amines mainly by CYP2C19, but also by CYP1A2, CYP2C9, and CYP3A4, while both tertiary and secondary undergo parallel hydroxylation reactions mainly by CYP2D6, with CYP2C19 making a lesser contribution (Aitchison, 2003; Bertilsson, 2007; Bertilsson et al., 2002). The secondary amine metabolites of amitriptyline and imipramine are nortriptyline and desipramine, respectively, each also available as licensed medications.

Using hepatic microsomes of varying CYP2C19 activity and recombinant CYPs, (Koyama et al., 1997) demonstrated that imipramine *N*-demethylation was catalyzed by CYP2C19 and CYP1A2 (high affinity and low affinity components, respectively), imipramine 2-hydroxylation was mediated by CYP2D6 and CYP2C19 (high affinity and low affinity components, respectively), and that in individuals deficient in CYP2C19, CYP1A2, and

CYP2D6 play a major role in imipramine *N*-demethylation and 2-hydroxylation respectively. Among the recombinant human CYPs, CYP2C19, 2C18, 2D6, 1A2, 3A4, and 2B6 in rank order catalyzed the *N*-demethylation, whereas CYP2D6, 2C19, 1A2, 2C18, and 3A4 catalyzed the 2-hydroxylation. In a monoclonal antibody inhibition, (Yang et al., 1999) concluded similarly that imipramine was metabolized to 2-hydroxyimipramine by 2C19 and 2D6, and to desipramine by 1A2, 2C18, 2C19, and 2D6, with the contributions of the isoforms to desipramine formation varying for 2C19 (13–50%), 1A2 (23–41%), and 3A4 (8–26%).

Tricyclic antidepressants inhibit presynaptic noradrenaline (also known as norepinephrine) and serotonin reuptake via the noradrenaline and serotonin transporters, respectively, with the tertiary amines having a greater affinity for the serotonin transporter than the secondary amines, which are relatively selective for the noradrenaline transporter (Owens, 1996). The tertiary amines are therefore SNRIs, while the secondary amines are noradrenaline reuptake inhibitors (or NARIs). There are also contrasts in their CYP inhibition. Tertiary amines TCAs (e.g., amitriptyline, imipramine) inhibit CYP2C19 (estimated Ki of 37.7 and 56.8 μM, respectively). By contrast, the secondary amines show negligible CYP2C19 inhibition activity (Shin et al., 2002) but inhibit CYP2D6 slightly more than tertiary amine TCAs; for example, estimated Ki values for the tertiary amine TCAs amitriptyline and imipramine are 31.0 and 28.6 μM, respectively, with Ki s for nortriptyline and desipramine being 7.9 and 12.5 (Shin et al., 2002). Although therapeutic plasma concentrations are less than 1 μM (Aitchison et al., 2010; Yau et al., 2007), cerebral concentrations may be higher (Aitchison et al., 2010; Weigmann et al., 2000). Further, this differential may be affected by factors such as p-gp expression at the blood–brain barrier. It is therefore possible that with repeated dosing, as the concentration of a tertiary amine TCA increases in the brain, that the level of CYP2C19 inhibition increases, and that this

leads to reduction in the demethylation reaction centrally. This would be expected to be associated with a greater degree of dual reuptake inhibition and may at least partly explain the clinical observation of time for antidepressant effect to maximize. This hypothesis is consistent with a report of an inverse relationship between CYP2C19 activity and response to TCAs (mainly tertiary amines, Aitchison et al., under revision).

There are also contrasts between the tertiary and secondary amines and side effect/adverse drug reaction potential. The side effects are associated with antagonism at the following receptors: adrenergic α1 and α2 receptors, muscarinic (cholinergic) receptors, and histamine H1 receptors (Cusack et al., 1994; Owens et al., 1997; Sanchez et al., 1999). Specifically, blockade of muscarinic receptors in the parasympathetic nervous system is associated with dry mouth, blurred vision, constipation, urinary retention, and if at toxic levels, delirium; alpha adrenergic receptor antagonism is associated with orthostatic hypotension; and histamine H1 receptor blockade with sedation and weight gain. Other side effects (such as palpitations, vertigo, sweating, tremors, and interference with sexual function) may also occur (Asberg et al., 1970; Hodgson et al., 2015; Uher et al., 2009b; Ziegler, 1978) and may represent more than one pharmacodynamic mechanism. The tertiary amine TCAs have greater cholinergic receptor binding than the secondary amines, which in turn have greater affinity than the hydroxylated metabolites (Rudorfer et al., 1999). Some effects may be related to specific metabolites (e.g., *N*-methyl quaternary ammonium derivatives of amitriptyline, doxepin, and imipramine are antagonists at both central nervous system and cardiac muscarinic receptors) (Ehlert et al., 1990). Hydroxylated metabolite concentration has been associated with increased QTc interval (Schneider et al., 1988; Stern et al., 1991). It is therefore possible that *CYP2D6* UM might have elevated hydroxy-metabolite plasma concentrations (Bertilsson et al., 1985) resulting

in an increased risk of cardiotoxicity. Moreover, TDM does not usually include measuring hydroxylated metabolite plasma concentrations. In the case of a combination of *CYP2C19* PM status and *CYP2D6* UM status, it might be advisable to avoid TCA prescription; this is in fact the CPIC recommendation for this combination (Hicks et al., 2017).

The association between *CYP2D6* and *CYP2C19* genotype and clinical response to TCAs (treatment efficacy and/or side effects) has been reviewed (Hicks et al., 2017). In brief, studies support the existence of a concentration–effect relationship for TCAs and/or their active metabolites (Gram et al., 1984; Perry et al., 1987; Preskorn et al., 1990; Sjoqvist et al., 1980; Ziegler et al., 1977b). In an early report, high concentrations of nortriptyline were linked to adverse effects, with decreased antidepressant effect (Asberg et al., 1970). Concentration-dependent side effects have been observed in individuals deficient in CYP2D6 when treated with usual doses of TCAs from accumulation of the parent drug and/or active metabolites (Balant-Gorgia et al., 1989; Bertilsson et al., 1981; Sjoqvist et al., 1984). Ethnic groups with a higher frequency of *CYP2D6* IM alleles achieve higher levels of TCAs than Whites and have a faster rate of recovery from depressive episodes (Raskin et al., 1975; Rudorfer et al., 1982; Ziegler et al., 1977a). An excess of *CYP2D6* PM alleles has been found in patients with a history of adverse reactions to TCAs and relevant SSRIs (Chen et al., 1996). *CYP2D6* PMs have high levels of desipramine, associated with adverse effects necessitating dose reduction (Spina et al., 1997). An inverse correlation between the frequency of adverse drug events and number of functional *CYP2D6* genes has been found, including patients on TCAs (Chou et al., 2003). In addition to the publication of the Hicks et al. (2017) review, other studies on the topic have been published such as Hodgson et al. (2015).

There are guidelines by both CPIC and DPWG (Bank et al., 2018a). CPIC guidelines for *CYP2D6* are as follows: for both PMs and UMs, it is suggested to avoid use of TCAs due to possible side effects or subthreshold concentrations, respectively. In both cases, when TCAs are still prescribed, TDM is recommended, with PMs starting at 50% regular dosage and for UMs consideration being given to use TDM to titrate up to a higher target dose. The DPWG provide specific suggested increases in the starting dosages for amitriptyline, clomipramine, doxepin, imipramine, and nortriptyline of 125, 150, 200, 170%, respectively followed by TDM (Bank et al., 2018a). For *CYP2D6* IMs, a 25% reduction in the initial dose is recommended by CPIC. For many drugs, evidence is still accumulating, and therefore implementation of the recommendations is "optional," or at prescriber discretion.

In regard to *CYP2C19* status, there are CPIC guidelines for the tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. For *CYP2D6* UMs, RMs, or PMs, CPIC provides an optional recommendation to substitute with medications not metabolized by CYP2C19, such as nortriptyline or desipramine. In the case of *CYPC19* PMs, a 50% decrease in initiation dose is suggested, with TDM to guide titration (Hicks et al., 2017).

There are also CPIC guidelines for amitriptyline where both *CYP2D6* and *CYP2C19* data are available. If an individual is a *CYP2D6* or *CYP2C19* PM and a NM for the other enzyme, it is recommended to avoid the medication or, if warranted, consider a 50% decrease in initiation dose; for a *CYP2D6* UM and *CYP2C19* NM, it is recommended to avoid the medication or, if warranted, consider titrating to a higher target dose (compared to *CYP2D6* NMs); and for a *CYP2D6* IM and *CYP2C19* NM, to consider a 25% decrease in initiation dose (Hicks et al., 2017). No adjustments in dosage is necessary for those who are NMs for *CYP2D6* and *CYP2C19*, or an NM for *CYP2D6* and an IM for *CYP2C19* (Hicks et al., 2017).

2.6.3.2 Tetracyclic Antidepressants

Mirtazapine acts as antagonist at adrenergic α2-autoreceptors and α2-heteroreceptors as well as at 5-HT2 and 5-HT3 receptors (Anttila et al., 2001). The α2-autoreceptor blockade leads to increased release of noradrenaline while the blockade of α2-heteroreceptor on serotonergic neurons increases serotonin release. Owing to antagonism of 5-HT2 and 5-HT3, transmission is enhanced at only 5-HT1A (and related receptors). It is a racemic mixture of R(−) and S(+)-enantiomers, with effects on heart rate and blood pressure correlating more strongly with R (−) than with S (+) concentration, and sedation being associated with both enantiomers (Brockmoller et al., 2007). The main metabolic pathway for mirtazapine is 8-hydroxylation, catalyzed mainly by CYP2D6 (65%) at low concentrations, reducing to 20% at higher concentrations, where CYP1A2 (50%), CYP3A4 (20%), and CYP2C9 (10%) contribute more (Dahl et al., 1997; Stormer et al., 2000). Other metabolic pathways are *N*-demethylation and *N*-oxidation. The former is conducted mainly by CYP3A4 (50–70%), with CYP1A2 (50% at low concentrations, 5% at high concentrations), CYP2C8 (<20%), and CYP2C9 (<5%) also contributing. N-oxidation is catalyzed by CYP1A2 and CYP3A4, with the former playing a larger role (80%) at low concentrations and the latter being responsible for a greater proportion (85%) of the reaction at higher drug concentrations (Dahl et al., 1997; Stormer et al., 2000). Enzyme polymorphism may additionally affect the relative contributions of these CYPs.

The maximum concentration and area under the curve are greater in females as compared to males (Sennef et al., 2003; Timmer et al., 2000). In non-smokers and at lower concentrations of mirtazapine, CYP2D6 genotype affects the plasma levels and clearance of the S-enantiomer and its metabolites (Brockmoller et al., 2007; Hayashi et al., 2015; Jaquenoud Sirot et al., 2012; Stormer et al., 2000). At higher concentrations (250 μM), CYP3A4 contributes to about 70%, while CYP2D6, CYP2C8, CYP2C9, and CYP1A2 each account for less than 15% of its

metabolism (Stormer et al., 2000). Unlike the tricyclics, there is no clear relationship between mirtazapine plasma concentration and its efficacy. While an increase in the maximal serum concentration for co-administered amitriptyline has been described (Sennef et al., 2003), the overall inhibitory effect of mirtazapine on CYPs is not thought to be clinically significant (Anttila et al., 2001; Spina et al., 2008). In the Sennef et al. (2003) study, co-administered amitriptyline increased the maximum concentration of mirtazapine (by 36%) in only males. S-hydroxymirtazapine concentration has been reported as being elevated in individuals of *CYP2B6∗6/∗6* genotype (Jaquenoud Sirot et al., 2012). As yet, there are no DPWG or CPIC guidelines for mirtazapine based on genotype.

2.6.3.3 Selective Serotonin Reuptake Inhibitors

The second SSRI to be synthesized, fluoxetine was the first SSRI to enter widespread use (Wong et al., 1975; Wong et al., 1974). Selective serotonin reuptake inhibitors are now widely used to treat depression, escitalopram having the highest affinity for the serotonin transporter (Owens et al., 2001) and being an allosteric modulator, one molecule increasing the binding of a second at this target.

In brief, SSRIs are partly metabolized by CYP2D6 (Brosen, 1993). Demethylenation is the initial step of paroxetine metabolism (an SSRI), primarily conducted by CYP2D6 (a high affinity saturable process, (Bloomer et al., 1992)). Further conjugation of paroxetine results in glucuronide and sulfate conjugated metabolites (Haddock et al., 1989). Paroxetine is a potent competitive inhibitor of CYP2D6 (Bourin et al., 2001) nonetheless, differences in steady-state plasma concentration of paroxetine by *CYP2D6* phenotype are seen (Gex-Fabry et al., 2008). Higher doses of paroxetine (e.g., 30 mg) are associated with a greater degree of CYP2D6 inhibition (Findling et al., 2006). In diabetic neuropathy, paroxetine has an analgesic effect,

plasma concentrations greater than 300–400 nmol/l being associated with optimal response (Sindrup et al., 1990; Sindrup et al., 1991).

Fluoxetine is a racemic mixture of S(+) and R(−)-fluoxetine, with the former being metabolized predominantly by CYP2D6 to S-norfluoxetine and the latter by CYP2D6 and CYP2C9 to R-norfluoxetine; CYP3A4 and CYP2C19 make minor contributions to this demethylation reaction (Hicks et al., 2015). R/S-fluoxetine and S-norfluoxetine are all potent SSRIs, with R-norfluoxetine being 20 times less potent (Hicks et al., 2015). The strength of CYP2D6 inhibition for SSRIs is as follows in reducing order: paroxetine, fluoxetine, norfluoxetine, desmethylcitalopram, fluvoxamine, sertraline, citalopram (Baumann et al., 1995). Although fluoxetine is less potent as an inhibitor of CYP2D6 than paroxetine, owing to its substantially longer half-life – 1–3 days and 4–6 days after acute and chronic administration, respectively, with the corresponding values being 4 and 16 days for norfluoxetine,[25] inhibition effects may endure for weeks to months after multiple dosing (Liston et al., 2002). Fluoxetine and sertraline also inhibit CYP2C19 (Bertilsson et al., 1996) while norfluoxetine is a moderate CYP3A4 inhibitor (Hemeryck et al., 2002).

The primary route of metabolism for citalopram (a racemic mixture of the R- and S-enantiomers of citalopram) and escitalopram (S-citalopram) is N-demethylation by CYP2C19, CYP2D6, and CYP3A4 (Kobayashi et al., 1997; Rochat et al., 1997; Sindrup et al., 1993; von Moltke et al., 2001). CYP2D6 then conducts the N-demethylation of N-desmethylescitalopram to N-didesmethylescitalopram (von Moltke et al., 2001). The medication and its metabolites may inhibit enzymes: citalopram and R- or S-desmethylcitalopram are weak inhibitors of CYP2C19, while R- and S-didesmethylcitalopram are moderate inhibitors, with mean IC50 values of 18.7

[25] https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018936s076lbl.pdf

and 12.1 μM, respectively. S-citalopram and S-desmethylcitalopram are weak inhibitors of CYP2D6 (IC50 = 70–80 μM); R-desmethylcitalopram shows stronger inhibition at this enzyme (IC50 25.5 ± 2.1 μM) (von Moltke et al., 2001). Fluvoxamine is predominantly a CYP1A2 inhibitor (Christensen et al., 2002) but also inhibits other CYPs including the CYP3As (Hemeryck et al., 2002). In a study, it was found that quinidine, a CYP2D6 inhibitor, significantly affected the synthesis of a metabolite of fluvoxamine, fluvoxamino alcohol (Miura et al., 2007). Another study that saw a relationship between cigarette smoking and *CYP2D6* PM status with oral clearance of fluvoxamine stablished the role of CYP2D6 as the major pathway for its metabolism and CYP1A2 as a minor pathway for metabolism of this SSRI (Spigset et al., 2001).

SSRIs are more 20 to 1500-fold more selective for inhibiting serotonin than noradrenaline. They do not stimulate the release of serotonin or norepinephrine presynaptically (Rothman et al., 2001) and have weak/no-direct pharmacological action at postsynaptic serotonin receptors (e.g., 5-HT1A, 5-HT2A, and 5-HT2C) (Owens et al., 1997; Sanchez et al., 1999; Thomas et al., 1987), and minimal binding affinity for other postsynaptic receptors (adrenergic α1, α2, and β, histamine H1, muscarinic, and dopamine D2 receptors) (Owens et al., 1997; Thomas et al., 1987).

Associations between SSRI phenotypes (concentrations, efficacy, tolerability) and *CYP2D6* and *CYP2C19* genotypes are provided in Supplementary Tables S7–S11 in Hicks et al. (2015). In a meta-analysis of the main functional CYP2C19 variants in Whites (the *CYP2C19*2* and the *CYP2C19*17*, plus wild-type by exclusion of these) for individuals treated with citalopram or escitalopram (in the GENDEP, STAR*D, GenPod, and PGRN-AMPS studies), *CYP2C19* PMs had greater symptom improvement and higher remission rates compared to NMs

(Fabbri et al., 2018). This is consistent with earlier data indicating that *CYP2C19* PMs respond better to escitalopram if treatment is tolerated (Mrazek et al., 2011). At weeks 2–4, PMs showed increased risk of side effects (Fabbri et al., 2018). In a retrospective analysis of data from 2087 patients treated with escitalopram and genotyped for *CYP2C19*, PMs had an increase in exposure and a higher rate of treatment dropout compared with *CYP2C19* NMs (Jukic et al., 2018). Conversely, the *CYP2C19∗17* haplotype was associated with an increase in CYP2C19 activity by approximately 20%, with those of *CYP2C19∗1/∗17* and *CYP2C19∗17/∗17* genotype showing a 50% increase in treatment failure rate compared with NMs (Jukic et al., 2018). Moreover, replicated findings that *CYP2C19* UMs treated with escitalopram exhibit increased suicidal ideation (Jukic et al., 2017; Rahikainen et al., 2019) indicates that distinguishing between *CYP2C19* NMs and UMs is clinically relevant for the escitalopram treatment. Using a combinatorial PGx algorithm (covering several different genes), researchers reported a significant association with variation in the metabolism of escitalopram/citalopram (Shelton et al., 2020).

The CPIC guidelines for SSRIs (Hicks et al., 2015) cover two medications for CYP2D6: paroxetine and fluvoxamine. The recommendation for paroxetine in the case of *CYP2D6* UMs is to select an alternative drug and likewise for PMs, with implementation being optional for the latter. For fluvoxamine, in the case of *CYP2D6* UMs there was insufficient data for a recommendation, with an optional recommendation to consider a 25–50% reduction in the starting dose for *CYP2D6* PMs, and titrate to response, or consider using an alternative medication not metabolized by CYP2D6.

Three medications are included in the CPIC SSRI guidelines in regard to CYP2C19: citalopram, escitalopram and sertraline. A 50% reduction of the standard dosage for the three

drugs is recommended for PM status, with and titration to response, or considering using an alternative medication not metabolized by CYP2D6 (strength of the recommendation being moderate for citalopram and escitalopram and moderate for sertraline). For *CYP2C19* UMs, for citalopram and escitalopram, selection of a medication not metabolized by CYP2C19 is recommended, while for sertraline, initiation at the normal dose may be tried, with substitution being considered if patients do not respond to treatment. The recommendations are classified as moderate for citalopram/escitalopram and optional for sertraline (Hicks et al., 2015).

In addition to the CPIC guidelines, other literature suggests that in the case of fluoxetine (not included in the guidelines above), due to its role as both substrate and inhibitor of CYP2D6, physicians should be careful if co-prescribing it with other CYP2D6 substrates (Stingl et al., 2013).

2.6.3.4 Serotonin Noradrenaline Reuptake Inhibitors

Venlafaxine is a SNRI, which means that like the tertiary amine tricyclics, it inhibits neurotransmitter reuptake at both the serotonin and noradrenaline (also known as norepinephrine) transporters. The major metabolic route for venlafaxine is *O*-demethylation, which is mediated very specifically by CYP2D6 to an active metabolite, *O*-desmethylvenlafaxine (Otton et al., 1996). The *N*-demethylation is conducted by CYP3A4 and CYP2C19 (Sangkuhl et al., 2014). This means that the ratio of the *O*- and *N*-demethylated metabolites of venlafaxine may in fact be used as a biomarker of CYP2D6 activity, predicting *CYP2D6* poor metabolizers with a specificity and sensitivity of >85% (Mannheimer et al., 2016). In in vitro studies, venlafaxine is a weaker inhibitor of CYP2D6 than are the SSRIs paroxetine, fluoxetine, fluvoxamine, and sertraline, and has minimal or no effect on CYP1A2, CYP2C9, and CYP3A4 (Ball et al., 1997; von Moltke et al., 1997). In a study of 1003 Scandinavians (mostly White), it

was found that CYP2D6 metabolism measured as the *O/N*-desmethylvenlafaxine ratio was significantly lower in carriers of *CYP2D6*41* vs. *CYP2D6*9–10* (Jukic et al., 2019). The annotated DPWG guideline states that for CYP2D6 poor (PM) and intermediate metabolizers (IM), select an alternative to venlafaxine or reduce the dose and monitor patient's plasma metabolite level; for CYP2D6 ultrarapid metabolizers (UM), increase dose to 150% of the normal dose or select an alternative to venlafaxine.[26]

Duloxetine acts as a serotonin and noradrenaline reuptake inhibitor, and a weak dopamine reuptake inhibitor (e.g., in the frontal cortex).[27] CYP1A2 and to a lesser extent CYP2D6 convert duloxetine into its main metabolites 4-hydroxy and 5-hydroxy duloxetine; activity (Knadler et al., 2011). CYP1A2 inducers including cigarette smoke therefore result in a reduction in duloxetine concentration (Augustin et al., 2018).

2.7 Atomoxetine

Atomoxetine is a noradrenaline reuptake inhibitor used as second-line in the treatment of ADHD. It is metabolized mainly by CYP2D6 to 4-hydroxyatomoxetine and by CYP2C19 to N-desmethylatomoxetine, which is subsequently metabolized via CYP2D6 to N-desmethyl-4-hydroxyatomoxetine (Atomoxetine)[28]. Other enzymes (CYP1A2, CYP2B6, CYP2C19, CYP3A4, and CYP2E1) also contribute to the hydroxylation, with glucuronidation occurring subsequently (Yu et al., 2016).[29] Atomoxetine may take 2-4 weeks for its full effect to be seen (Savill et al., 2015); peak concentrations have been associated with treatment efficacy and *CYP2D6* genotype has been associated with both peak concentration and half-life (e.g., exposure is on average 10-

[26] https://www.pharmgkb.org/chemical/PA451866/guidelineAnnotation/PA1661049
[27] https://stahlonline.cambridge.org/prescribers_drug.jsf?page=9781316618134c40.html.therapeutics&name=Duloxetine&title=Therapeutics
[28] https://www.pharmgkb.org/chemical/PA134688071
[29] https://www.pharmgkb.org/chemical/PA134688071

fold greater in *CYP2D6* PMs; reviewed in the CPIC atomoxetine guidelines, (Brown et al., 2019)). Individuals homozygous for the *CYP2D6∗10* haplotype show a 5-fold higher peak atomoxetine concentration compared with individuals with at least one normal function haplotype; individuals heterozygous for the *CYP2D6∗10* also had higher atomoxetine exposure compared with *CYP2D6* NMs (Byeon et al., 2015; Cui et al., 2007; Matsui et al., 2012).

The initiation dose for children and adolescents 0.5mg/kg/day. For UMs, NMs and IMs without a *CYP2D6*10*, after three days an increase in dose to 1.2mg/kg/day is recommended. At the two-week point, if there is neither efficacy nor adverse events, measurement of peak concentration 1–2 h after dose should be considered, and should this be less than 200 ng/ml, the dose may be increased until the concentration reaches 400 ng/ml. For those with an activity score of 0 (PMs), 0.5–1.0 (IMs including those with a *CYP2D6*10*) the recommendation is that if there is neither efficacy nor adverse events by two weeks, to consider measuring plasma concentration 2–4 h (4 h for PMs) after dosing; if response is inadequate and the concentration is less than 200 ng/ml, the dose may be increased to approach 400 ng/ml; while if unacceptable side effects are present at any time, a reduction in dose should be considered. Of note, while the strength of the evidence for IMs, NMs, and UMs is moderate, for PMs, it is strong (Brown et al., 2019).

For adults, the starting dose is 40 mg/day. For UMs, NMs and IMs without a *CYP2D6∗10*, the dose should be increased to 80 mg/day after three days; if there is neither efficacy nor adverse events at two weeks, it is recommended to consider increasing the dose to 100 mg/day. After a further two weeks, if there is no clinical response, measurement of peak concentration 1–2 h after dose should be considered, and should this be less than 200 ng/ml, the dose may be increased until the concentration reaches 400 ng/ml. Doses above 100 mg/day may be needed to achieve target concentrations. For those with an activity score of 0, or 0.5–1.0 (IMs

including those with a *CYP2D6∗10*), the recommendation is that if there is neither efficacy nor adverse events, at two weeks increase the dose to 80 mg/day. If resultant efficacy is inadequate, consideration should be given to measuring plasma concentration 2–4 h (4 h for PMs) after dosing; if the concentration is less than 200 ng/ml, the dose may be increased to approach 400 ng/ml; while if unacceptable side effects are present at any time, a reduction in dose should be considered.

To date one paper shows an association between CYP2C19 and atomoxetine pharmacokinetics, with PMs showing higher atomoxetine concentration and half-life, and with correspondingly lower values for N-desmethylatomoxetine (Choi et al., 2014). Replication of this is required before any guidelines result.

2.8 Conclusion

Many genetic variants in drug metabolizing enzymes and transporters have been shown to be relevant for psychiatry. Associations are strong enough to feature on drug labels and for prescribing guidelines based on such data (CPIC; DPWG). The International Society of Psychiatric Genetics recommends *HLA-A* and *HLA-B* testing prior to use of carbamazepine and oxcarbazepine, and suggests that genetic information for *CYP2C19* and *CYP2D6* would be likely to be most beneficial for individuals who have experienced insufficient efficacy or an adverse reaction to a previously tried antidepressant or antipsychotic (ISPG, 2019). A range of (non-validated) commercial tests are currently available; however, there is variability in included genetic variants, methodology, and interpretation. This variability presents challenges for clinicians and other end users. Maruf and colleagues suggest the following should be considered: (a) whether or not the lab is accredited; (b) the relevance of the genetic variants to the medications of interest; (c) test logistics (such as turnaround time) (Maruf et al., 2020). With

genes such as *CYP2D6* that are particularly challenging, a pragmatic approach may need to be taken: balancing a desire for a fast turnaround in a clinically accredited laboratory with a comprehensive coverage of all relevant functional variants.

While considerable progress has been made in determining reference samples (Gaedigk et al., 2019), what is still required is a consensus regarding the minimum set of informative variants in relevant genes that should be genotyped, methodologies for genotyping these efficiently and in a validated manner, and standardized interpretation with reporting algorithms and decision-support tools that can be integrated into electronic medical records. In addition, there has been relatively little work to date clinical associations with genetic variants in more than one gene (Greden et al., 2019; Hicks et al., 2017). Depression was predicted to be responsible for the greatest global burden of disease by 2030 (Malhi et al., 2018) and in fact, given the evidence of increasing prevalence in association with the current viral pandemic (Galea et al., 2020; Holmes et al., 2020), this may be an underestimate. Depression is the mental health condition with the most prescribing guidelines in association with gene–drug pairs. Pharmacogenetically informed care has the potential to enhance treatment efficacy and reduce ADRs for this common disorder associated with not only the type of health burdens previously measured but also with a negative impact on outcomes from other health conditions ranging from cardiovascular to infectious diseases. Further, pharmacogenetics may not only reduce the risk of undesirable drug-drug interactions but may also in fact inform the utility of drug-drug interactions that may have a beneficial therapeutic effect – such as the induction of expression of *ABCB1* (Tian et al., 2005) (which may be associated with viral resistance). Significant ground in this area has been covered to date, but much remains to be covered. For example, ABCB1 would appear to be the CYP2D6 equivalent of drug transporters and is largely uncharted territory in

terms of specific genotype–phenotype relationships by substrate binding including cooperativity, inhibition, and induction.

2.9 Author Contributions

All authors contributed to manuscript drafting (each citation being reviewed by at least two authors), and approved the final version for publication.

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2.11 Conflict of Interest

KA is a member of the Pharmacogene Variation Consortium, Clinical Pharmacogenetics Implementation Consortium, has received two research grants in the last two years from Janssen Inc., Canada (fellowship grants for trainees) and provided consultancy services (unpaid) for HLS Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CHAPTER 3: Methodology for clinical genotyping of *CYP2D6* and *CYP2C19*

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3.1 Abstract

Many antidepressants, atomoxetine, and several antipsychotics are metabolized by the cytochrome P450 enzymes CYP2D6 and CYP2C19, and guidelines for prescribers based on genetic variants exist. Although some laboratories offer such testing, there is no consensus regarding validated methodology for clinical genotyping of *CYP2D6* and *CYP2C19*. The aim of this paper was to cross- validate multiple technologies for genotyping *CYP2D6* and *CYP2C19* against each other, and to contribute to feasibility for clinical implementation by providing an enhanced range of assay options, customizable automated translation of data into haplotypes, and a workflow algorithm. AmpliChip CYP450 and some TaqMan single nucleotide variant (SNV) and copy number variant (CNV) data in the Genome-based therapeutic drugs for depression (GENDEP) study were used to select 95 samples (out of 853) to represent as broad a range of *CYP2D6* and *CYP2C19* genotypes as possible. These 95 included a larger range of *CYP2D6* hybrid configurations than have previously been reported using inter-technology data. Genotyping techniques employed were: further TaqMan CNV and SNV assays, xTAGv3 Luminex CYP2D6 and CYP2C19, PharmacoScan, the Ion AmpliSeq Pharmacogenomics Panel, and, for samples with *CYP2D6* hybrid configurations, long-range polymerase chain reactions (L-PCRs) with Sanger sequencing and Luminex. Agena MassARRAY was also used for *CYP2C19*. This study has led to the development of a broader range of TaqMan SNV assays, haplotype phasing methodology with TaqMan adaptable for other technologies, a multiplex genotyping

method for efficient identification of some hybrid haplotypes, a customizable automated translation of SNV and CNV data into haplotypes, and a clinical workflow algorithm.

3.2 Introduction

Many antidepressants, atomoxetine, and several antipsychotics are metabolized by CYP2D6 and CYP2C19 (Aitchison et al., 2000c; Carvalho Henriques et al., 2020; DPWG, 2019; Hicks et al., 2017; Hicks et al., 2013; Jukic et al., 2018; Lapentina et al., 2020). The gene (*CYP2D6*) encoding the enzyme CYP2D6 is on chromosome 22q13.2 (Gough et al., 1993) adjacent to two pseudogenes, *CYP2D7* and *CYP2D8* (Kimura et al., 1989; Nofziger et al., 2020). The high homology between *CYP2D6* and these pseudogenes and the presence of flanking transposable genetic elements (Yasukochi et al., 2011) makes the region vulnerable to the generation of variable copy numbers of the *CYP2D6* gene and hybrid genes made up of sequence derived in part from *CYP2D7* and in part from *CYP2D6* (Black et al., 2012; Daly et al., 1996; Gaedigk et al., 2008; Gaedigk et al., 2010a; Gaedigk et al., 2018; Gaedigk et al., 2010b; Kramer et al., 2009; Panserat et al., 1995; PharmVar, 2021b). Such variants are challenging to characterize for many technologies. The *CYP2C19* gene encoding the CYP2C19 enzyme is located at chromosome 10q23.33, also together with other similar genes (Botton et al., 2021; Chen et al., 2009; Goldstein et al., 1994; Nelson et al., 2004). While structural variants of *CYP2C19* have recently been identified (Botton et al., 2019), the more commonly studied haplotypes result from single nucleotide variants (SNVs) (PharmVar, 2021a). Haplotypes in both genes are referred to as “star

alleles," e.g., **2, *3*, etc. as defined by PharmVar, a consortium which maintains a curated catalog of allelic variation in genes impacting drug metabolism, disposition, and response.

Different *CYP2D6* or *CYP2C19* haplotypes may be associated with different levels of enzyme activity, ranging from loss-of- function haplotypes (which give rise to no functional enzyme), to haplotypes with decreased function (which are associated with an enzyme with reduced metabolic activity), to gain-of-function haplotypes (associated with increased activity) (Carvalho Henriques et al., 2020). Haplotype frequencies vary between and within ethnic groups (Aitchison et al., 2000c; Carvalho Henriques et al., 2020; PharmGKB, 2021b, 2021c, 2021d, 2021e). The study of clinical associations between variants in these genes and response to relevant medications has been to date limited by the challenging nature of the genotyping, particularly in the case of *CYP2D6* (Nofziger et al., 2018). This gene is extremely polymorphic, with single or short sequence variants including indels (insertions/deletions), sequence derived from *CYP2D7* (described as "conversions" such as an exon 9 conversion), and structural variants (deletions of the entire *CYP2D6* gene, gene duplications/multiplications denoted as *xNs*, and hybrids (PharmVar, 2021b) as above described).

There are now a number of laboratories offering testing for these genes for clinical utility; however, to date there is no consensus regarding validated methodology suitable for this purpose (Bousman et al., 2018b). Clinical validation requires selecting appropriate haplotypes for testing, obtaining reference samples, and establishing test analytical validity and feasibility (Bousman et al., 2021). A recent paper provides recommendations on *CYP2D6* haplotype selection for clinical testing (Pratt et al., 2021), and the Genetic Testing Reference Material Program (GeT-RM) has conducted extensive work in order to provide reference samples (Gaedigk et al., 2019; Pratt et al., 2016; Pratt et al., 2010). The aims of this paper were to cross-validate multiple technologies

against each other for genotyping *CYP2D6* and *CYP2C19* thereby facilitating feasible clinical implementation through the provision of a range of assay options, to develop customizable and automated translation of data into haplotypes, and to recommend an efficient clinical workflow algorithm that includes hybrid configurations. CYP2D6 metabolizes many other medications in addition to psychotropics (in total ~20–25% of clinically used drugs (Ingelman-Sundberg, 2005; Saravanakumar et al., 2019; Zanger et al., 2013)); this work is also relevant for these medications, many of which are prescribed as comedications in patients with psychiatric disorders.

In the GeT-RM publications, data are available from the AmpliChip CYP450 Test, the Luminex CYP2D6 xTAG v3, and other genotyping platforms including AutoGenomics INFINITI, ParagonDx, and LDT SNaPShot, PharmacoScan, Agena MassARRAY iPLEX CYP2D6 v1.1, TaqMan assays, L-PCR, digital droplet PCR, and amplicon sequencing using next-generation sequencing (NGS) or long-read single-molecule real-time sequencing (SMRT, N = 3) (Gaedigk et al., 2019; Pratt et al., 2016; Pratt et al., 2010). CYP2D6 TaqMan assays have been compared with data arising from mPCR-RETINA, Sanger sequencing, long-PCR for *CYP2D6*5*, and NGS data available via the 1000 Genomes Project (Fang et al., 2014). Validation data have been provided for the Agena VeriDose Core and CYP2D6 copy number variation (CNV) Panel versus a proprietary panel and two TaqMan assays (Kothary et al., 2021). There are two technologies that provide SMRT sequencing: Pacific Biosciences and Oxford Nanopore; the former has been compared to data for *CYP2D6* from the AmpliChip CYP450 Test (which included 32 CYP2D6 variant haplotypes including some structural variants but no hybrids) on 25 individuals in one study (Buermans et al., 2017), and to data from targeted Illumina NGS in 17 individuals including one hybrid haplotype (CYP2D6*36) (Fukunaga et al.,

2021); the latter has been used on 7 reference and 25 clinical samples (which included some structural variants but no hybrids) (Liau et al., 2019). The former was also applied to 561 patients with breast cancer, and to replication samples, although with limitations, including pertaining to hybrid haplotypes (van der Lee et al., 2021). While software exists to call *CYP2D6* haplotypes from next generation full sequencing data (Chen et al., 2021; Lee et al., 2019; Twesigomwe et al., 2020; Twist et al., 2016), such tools are not yet available for SMRT data, or for combinations of CNV and SNV data that arise from other technologies including NGS.

The novel contributions described herein include: (1) inter- technology concordance data on genotypes from genomic samples including a range of *CYP2D6* hybrids and hybrid tandems for the AmpliChip CYP450 test, TaqMan CNV and SNV assays, the Luminex CYP2D6 and CY2C19 xTAG v3 assays, the NGS AmpliSeq Pharmacogenomics Panel, PharmacoScan, and the Agena MassARRAY (for *CYP2C19*); (2) details of *CYP2D6* amplicon Sanger sequencing methodology including primers; (3) adaptation of the Luminex CYP2D6 assay for amplicon sequencing and provision of concordance data for this versus Sanger sequencing so that other multiplex genotyping methods can also be adapted for efficient identification of hybrid haplotypes; (4) haplotype derivation files for the interpretation of combinations of *CYP2D6* CNV and SNV data including hybrids and *CYP2C19*; (5) development of a broader range of TaqMan SNV assays; (6) outline of haplotype phasing methodology with TaqMan adaptable for other technologies; and (7) a clinical workflow algorithm that includes hybrid configurations.

3.3 Materials and Methods

Ninety-five DNA samples (originating from venous blood) were selected from those previously genotyped for *CYP2D6* and *CYP2C19* using the AmpliChip CYP450 Test (Roche Molecular Systems, Pleasanton, USA) supplemented by the TaqMan assay C_469857_10 for *CYP2C19*17*

as part of the Genome-based therapeutic drugs for depression (GENDEP) study (Huezo-Diaz et al., 2012). Participants were all of self-reported White European ancestry. GENDEP was originally approved by ethics boards at all participating centers and approval for the work described herein was also provided by the University of Alberta Health Research Ethics Board—Biomedical Panel. Written informed consent was provided by all participants. The AmpliChip identified 32 CYP2D6 variant haplotypes (**2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40, *41, *114* (reported as **14A*) **1×N* (*×N* referring to more than one copy), **2×N, *4×N, *10×N, *17×N, *35×N, *41×N*). In addition, it covered *CYP2C19* haplotypes **2* and **3*. Sample DNA concentrations were ascertained using fluorimetry- based methods (Qubit or Quantifluor).

3.3.1 TaqMan Copy Number Variant (CNV) Assays for CYP2D6

TaqMan CNV assays for *CYP2D6* (assay IDs: Hs04083572_cn and Hs00010001_cn for intron 2 and exon 9 respectively; Thermo Fisher Scientific) were run according to the manufacturer's protocol on a ViiA7 Real-Time PCR System (Thermo Fisher Scientific). Assays were run in quadruplicate (Henriques et al., 2020). Data were analyzed using CopyCaller software version 2.1 (Thermo Fisher Scientific) with internal calibrators of known *CYP2D6* copy number according to the manufacturer's instructions (using a confidence level of at least 95%, most being above 99%).

Samples for which the TaqMan CNV call across the two probes were not equal and hence indicative of *CYP2D6* hybrids were analyzed with a third probe (assay ID Hs04502391_cn for *CYP2D6* intron 6). These samples, and those representing as broad a range of *CYP2D6* and *CYP2C19* genotypes as possible by the AmpliChip CYP450 and TaqMan *CYP2C19*17* assays, or "no call" for *CYP2D6* on the AmpliChip CYP450 were then taken forward for further analysis

(N = 95). The 95 were thus enriched for complex structural variants and other difficult to detect genotypes. The following genotyping techniques were employed: Luminex CYP2D6 xTAG v3 and Luminex CYP2C19 xTAG v 3, PharmacoScan (Thermo Fisher Scientific, Waltham, MA, USA), Ion AmpliSeq Pharmacogenomics Panel (Thermo Fisher Scientific), and TaqMan Drug Metabolism Genotyping Assays (Thermo Fisher Scientific). Data arising from these were then used to select samples for the generation of amplicons by long-range polymerase chain reaction (known as L-PCR) (Aitchison et al., 1999; Black et al., 2012; Gaedigk et al., 2010a; Gaedigk et al., 2007; Gaedigk et al., 2015).

3.3.2 TaqMan SNV assays

Haplotype phasing for samples with three copies of the CYP2D6 gene according to the TaqMan, Pharmacoscan, and/or AmpliSeq CNV probe data, and heterozygous SNV data was conducted by the following methodologies: TaqMan assays for the relevant CYP2D6 SNVs on genomic DNA, and/or L-PCR specific for *CYP2D6* duplicated genes followed by genotyping of the L-PCR product using relevant TaqMan SNV assays. The TaqMan SNV assays used were for *CYP2D6*2, *3, *4, *6, *35* and **41* (with assay IDs C_27102425_10, C_32407232_50, C_27102431_D0, C_32407243_20, C_27102444_F0, and C_34816116_20 respectively). The TaqMan SNV assays for *CYP2D6*2, *4, *10* (assay ID: C 11484460_40), and **35* were used on genomic DNA to conduct haplotype phasing for samples with CNV data consistent with three *CYP2D6* genes including a hybrid gene. In addition, a TaqMan assay (assay ID C 25986767_70) was used to cross-validate a *CYP2C19*2*-defining SNV, rs4244285. Samples were run in duplicate on a ViiA7 Real-Time PCR System (Thermo Fisher Scientific), with genotype calling after visual inspection, outlier exclusion, and manual adjustment of CT threshold settings as

necessary. Data arising from duplicates were compared with each other using an automated method available from the authors at request.

3.3.3 Luminex

The Luminex xTAG CYP2D6 and CYP2C19 Kits v3 (research use only versions) were run according to the manufacturer's instructions using a Luminex 200 system (Luminex Molecular Diagnostics, Inc., Toronto, ON, Canada). The assays use multiplex allele specific primer extension (ASPE) with a bead-based assay system. Haplotypes covered for *CYP2D6* are: *CYP2D6*2–*12* (including the **5* gene deletion), **14, *15, *17, *29, *35, *41*, and gene duplication. Multiple different CYP2D6 haplotype translators are provided (https://doi.org/10.6084/m9.figshare.16828741) owing to the Allele Typer software having a limit on the number of haplotypes that it can process in a given translator. These cover this range of haplotypes covered by the Luminex and also permit derivation of other haplotypes of known function (**20, *39.001, *39.002, *69, *114*) and sub-haplotypes (**1.011, *2.001/*2.005/*2.012/*2.013/*2.018/*2.020/*2.021, *2.004, *4.002, *4.012, *6.003, *12.001, *12.002*), hybrid haplotypes (**4.013*, two specific **13*s (EU093102 previously known as **66*, and GQ162807 previously known as **77*), **36, *57, *61, *63, *68*, and **83*) and hybrid tandems (**4.013 + *4, *4.013×2 + *4, *4.013 + *4 × 2, *4.013 × 2 + *4 × 2, *36 + *10, *36 + *10 × 2, *36 × 2 + *10, *36 × 2 + *10 × 2*). We also provide other versions of the translators in which **70* or **107* replace a **39* haplotype. These latter versions are intended for research use. The RUO software for *CYP2C19* reports *CYP2C19*2–*10*, and **17*. Our *CYP2C19* haplotype translator (https:// doi.org/10.6084/m9.figshare.16828738) also permits derivation of: **2.002/ *2.010/*2.012, *4, *4.002, *5, *6, *7, *8, *9*, and **10*.

3.3.4 Ion AmpliSeq pharmacogenomics panel

Genotyping using the Ion AmpliSeq Pharmacogenomics Panel (Thermo Fisher Scientific) was conducted according to the manufacturer's instructions using an Ion Chef instrument (Thermo Fisher Scientific, Waltham, MA, USA). Short stretches of genomic DNA were sequenced, including regions of CYP2D6 designed to detect *CYP2D6*-structural variants. Following sequencing, data were analyzed using the GeneStudio Data Analysis software (Thermo Fisher Scientific). Sequencing generated an average of 109,454 reads per sample (mean read length 142.5 bp), with two samples failing quality control (in a manner indicating likely insufficient template: mapped read numbers of 18 and 51). Variant calling by the Ion Torrent Variant Caller version 5.10.1.19 (Thermo Fisher Scientific) generated three text files: one with the genotype at each SNV (including 20 *CYP2D6* variants and 11 *CYP2C19* variants), one for the *CYP2D6* exon 9 CNV output, and one for the *CYP2D6* gene level CNV data (based on sequence across nine regions in *CYP2D6*) (https://doi.org/10.6084/m9.figshare.16828747). Haplotype translation files were created (using data from PharmVar, hybrid haplotype data available on the archived Human Cytochrome P450 (CYP) Allele Nomenclature Committee page (PharmVar, 2016), and a relevant publication (Kramer et al., 2009)) to derive *CYP2D6* and *CYP2C19* haplotypes including various hybrid configurations in conjunction with the AlleleTyper software (Thermo Fisher Scientific).

3.3.5 PharmacoScan

The PharmacoScan array-based technology was run at Neogen Genomics (Lincoln, NE, USA). The resultant data, including more than 100 variants in *CYP2D6* and 60 variants in *CYP2C19*, were analyzed using the Axiom Analysis Suite 4.0.3.3 (Thermo Fisher Scientific). Version r8 + 20200211 of the manufacturer's *CYP2D6* haplotype translation file was used. This file was created using data from PharmVar, building on earlier work that used data available on the

archived Human CYP Allele Nomenclature Committee page, and some contribution from the Aitchison laboratory. CNV calls were provided by probes for exon 9 of *CYP2D6* as well as for the 5′ and 3′ flanking regions as described (Gaedigk et al., 2019).

3.3.6 Long-range PCR Assays with Characterization of Resultant Amplicons

L-PCR was performed as described with minor modifications to generate an amplicon specific for the duplicated *CYP2D6* gene (Gaedigk et al., 2007). In brief, for the L-PCR assay that generates the D amplicon (specific for duplicated *CYP2D6* genes), we used primers as described (Gaedigk et al., 2007), i.e., forward and reverse 5′-CCAGAAGGCTTTGCAGGCTTCAG-3′ and 5′-CGGCAGTGGTCAGCTAATGAC-3′, respectively, with minor modifications to the PCR conditions. Amplicons were purified by gel extraction (GeneJET Gel Extraction Kit, Thermo Fisher Scientific, Waltham, MA, USA), and genotyped using the TaqMan SNV assays described above.

Samples with unequal calls across the TaqMan, PharmacoScan, or AmpliSeq CNV probes were subjected to L-PCR assays to generate amplicons specific for *CYP2D6-2D7* or *CYP2D7-2D6* hybrids (E, G (Black et al., 2012), or H (Gaedigk et al., 2010a)), with minor modifications. Amplicons were purified by gel extraction and subjected to Sanger sequencing (10 µl at 3.5 ng/µl per reaction) using BigDye Terminator version 3.1 chemistry, the Axygen CleanSEQ magnetic beads-based post-reaction clean up protocol (automated on a Biomek 3000 workstation), and a capillary 3130xl Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA).

Primers for sequencing (Supplementary Table 1A-C) included novel ones designed for this study, those supplied by Dr. Gaedigk (personal communication), as well as previously reported ones used to generate the L-PCR amplicons and in prior literature (Broly et al., 1995;

Gaedigk et al., 2015; Hosono et al., 2009). Sequence traces were aligned (to sequences available via the PharmVar (PharmVar, 2021c) or archived (PharmVar, 2016) *CYP2D6* pages) and analyzed using SnapGene software version 5.1.4.1 (GSL Biotech LLC, Chicago, IL, USA).

3.3.7 The Agena MassARRAY

The Agena MassARRAY (Agena Bioscience, San Diego, CA, USA) uses matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry technology for resolving oligonucleotides. We ran 8 *CYP2C19* variants to enable calling of 9 haplotypes. Genomic DNA was subjected to PCR followed by single-base extension with the extension products then being dispensed onto a SpectroCHIP Array and detected via mass spectrometry as described (Gaedigk et al., 2019). Haplotypes were assigned using Typer Analyzer software version v4.1.83 (Agena Bioscience).

3.4 Results

CYP2C19

Percentage concordance for Luminex, AmpliSeq, PharmacoScan, Agena, and prior data with consensus CYP2C19 genotype are shown in Table 3.1. All technologies apart from the AmpliChip were able to detect *CYP2C19*6* and **8*. For *CYP2C19*2* and *CYP2C19*17*, data from all technologies, where available, were concordant.

Table 3.1 Percentage concordance for Luminex, Ion S5, PharmacoScan, Agena, and prior data with consensus CYP2C19 genotype.

Consensus genotype	*N*	Prior data: AmpliChip[a] and TaqMan **17* (% concordance)	Luminex RUO (% concordance)	Ion S5 (% concordance)	PScan (% concordance)	Agena (% concordance)
**1/*1*	44	100	100	97.7 (42/43)[b]	100 (42/42)[c]	95.2 (40/42)[d]
**1/*17*	24	100	100	100 (22/22)	100 (23/23)	100 (22/22)
**1/*2*	16	100	100	100	100	100
**17/*17*	1	100	100	0(0/1)[e]	NA[f]	100
**2/*17*	4	100	100	100	100	100 (3/3)
**2/*2*	2	100	100 (1/1)	100[g]	100	100 (1/1)
**1/*8*	1	0	100	100	100	100
**2/*6*	1	0	100	100	100	100

For enhanced validation, two more samples of *CYP2C19*17/*17* genotype by TaqMan were genotyped: one on IonS5, PharmacoScan and Luminex (concordant on all three technologies), and one on Luminex (concordant). A TaqMan assay for *CYP2C19*2* cross-validated AmpliChip data 100% in the full GENDEP dataset.[a]Note that the overall concordance for the AmpliChip data without the *CYP2C19*17* by TaqMan was 64/96 = 66.7%. [b]One "no call" out of the 43 genotyped using this assay. [c]A couple of *CYP2C19*27* haplotypes were found in this group; this is now classified as *CYP2C19*1.006*. [d]Two "no calls" out of the 42 genotyped using this assay. [e]One "no call". [f]Not assayed. [g]Two samples for which the specific options were *2/*2.002, *2.010, *2.012.

CYP2D6

Comparative genotypic and CNV data across the technologies for samples with one and three copies of the *CYP2D6* gene are shown in Supplementary Tables 2 and 3, respectively. Owing to the "no calls" in the AmpliSeq CNV data, we revised these to manual calls, where possible, after reviewing the vcf files. This did result in an improvement in the degree of concordance with consensus genotypes for the AmpliSeq. Data for samples with a CNV call of two are shown in Supplementary Table 4.

While the AmpliChip provided haplotype phasing of *CYP2D6xNs* (i.e., assignment of the duplication/multiplication to one or other of the two chromosomes), the other technologies included herein do not offer that. We used TaqMan assays on genomic DNA to identify which haplotype was duplicated/multiplicated based on relative magnitude of signals arising from TaqMan wild-type and mutant probes for each assay (Supplementary Fig. 1). All of our *CYP2D6xNs* were duplications with the exception of one sample, which had a *CYP2D6*41×3*. Consistent with this, our TaqMan CNV data were 4, 4, 4, and the raw PharmacoScan copy number probe calls were 4, 4, 4.

Data including consensus genotypes for the samples with hybrids genotyped to date are shown in Supplementary Table 5. Nineteen samples had an unequal call across at least two out of three CNV probe sets (TaqMan, PharmacoScan, or AmpliSeq); for nine of these, the CNV pattern was consistent with a *CYP2D7-2D6* hybrid, and for 10 with a *CYP2D6–2D7* hybrid. For all of the *CYP2D6–2D7* hybrids, the pattern was consistent with an extra *CYP2D6* gene, either

on the same haplotype as the hybrid gene (in cis), or on the other chromosome 22 (in trans). This was also the case for five of the *CYP2D7–2D6* hybrids. Amplicons consistent with hybrids (Black et al., 2012; Gaedigk et al., 2010a; Gaedigk et al., 2010b; Kramer et al., 2009) were generated for all 19 samples. Six samples had an unequal call across CNV probes for only one platform; four of these were genotyped as CYP2D6 duplications (*CYP2D6*1×2/*4, *1/*1×2, *2×2/*1* and **2×2/*35*) and two as heterozygotes (**1/*2* and **1/*3.001*). For three of these, amplicon G was generated; however, it should be noted that the primer pair for this amplicon will also amplify up *CYP2D7* (Fig. 2 in Black et al. (2012), observed where the *CYP2D6* downstream gene was **1, *4,* or **41*; these three all had genotypes including the **1* and/ or **4*, specifically **1/*2, *1×2/*4, *4×2/*1*).

L-PCR amplicons specific for *CYP2D7–2D6* hybrids aligned well to *CYP2D6*13* sequences. Specifically, three samples aligned to the GQ162807 sequence (previously *CYP2D6*77*) deposited by Gaedigk et al. (2010), where *CYP2D6*13* is found in tandem arrangement with *CYP2D6*2*. The consensus genotype (from data including TaqMan assays) for these samples was *CYP2D6*13 + *2/*1*. Three other amplicons aligned well to the EU093102 sequence for another *CYP2D6*13* variant, which is found as a single gene on one chromosome (Daly et al., 1996; Gaedigk et al., 2008), consistent with the consensus genotypes for these samples: *CYP2D6*13/*4.013*, *CYP2D6*13/*1*, and *CYP2D6*13/*1* (Supplementary Table 5). At this point, we have two remaining *CYP2D6*13s* for which the exact *CYP2D6*13* has not been identified; however, we have sufficient data to make a consensus genotype call for both (*CYP2D6*13 + *4/*5*, and *CYP2D6*13 + *2/*41*) and all *CYP2D6*13* haplotypes have the same CYP2D6 enzyme activity score (zero, i.e., do not encode any functional CYP2D6 protein) owing to a T insertion in exon 1 that is a frameshift mutation resulting in premature chain

termination (PharmVar, 2021b). L-PCR amplicons for *CYP2D6-2D7* hybrids aligned to EU530605 (*CYP2D6*4-like* (Kramer et al., 2009)), with one aligning to EU530606 (partial sequence for *CYP2D6*68* (Kramer et al., 2009)).

*CYP2D6*13 + *4/*5* represents a novel haplotype. The CNV data from TaqMan and AmpliSeq were 1, 2, 2 and 1, 2 consistent with the presence of a *CYP2D7–2D6* hybrid (a *CYP2D6*13*) with a switch region between intron 2 and intron 6. On alignment of the Sanger-sequencing data, the sequence appeared as if the sample was heterozygous from a region consistent with this inferred switch region onwards, with the region prior to this aligning well to *CYP2D7*. This would be consistent with our long-PCR having amplified up both a *CYP2D7[REP6]* (a version of *CYP2D7* that has a *CYP2D6* version of the repeat element at its 3′ region, consistent with the 3′ primer used for the long-PCR) and a *CYP2D6*13* (legacy designations for the *CYP2D6*13* haplotypes *CYP2D6*67, *78*, and *80* (Aitchison et al., 2000c; Gaedigk et al., 2010a; Gaedigk et al., 2010b; PharmVar, 2016, 2021b) have switch regions in the relevant area. Comparative data from other technologies for this sample showed genotypes of *CYP2D6*4/*4* (AmpliChip), and no call with alternative calls of *CYP2D6*4/UNK* or *4.009/UNK* (Pharmacoscan). These indicate that a *CYP2D6*4* haplotype is also present. Haplotype phasing with the *CYP2D6*4* TaqMan assay indicated a deletion on one allele and the *CYP2D6*4* on the other. Therefore, we deduced a configuration of *CYP2D6*13 + CYP2D6*4/CYP2D6*5*, where the *CYP2D6*5* deletion has a *CYP2D7[REP6]* followed by a deletion of the *CYP2D6* gene.

We also subjected the L-PCR amplicons to genotyping using the Luminex CYP2D6 assay, with a protocol modification. The resultant genotypes at 14 SNVs were consistent with the sequence data (Table 3.2A, B). For example, the 4181G>C (rs1135840) variant was found in the

Luminex and sequence data for samples aligned to GQ162807 or EU093102, while the 2851C>T (rs16947) variant was wild type for samples aligned to EU093102 and variant for samples aligned to GQ162807. For the *CYP2D6–2D7* hybrids, our *CYP2D6* haplotype translator was able to identify hybrids including hybrid tandems (Supplementary Table 5).

3.5 Discussion

Consensus genotypes generated in 95 samples for *CYP2D6* and 93 samples for *CYP2C19* to date resulted in revision of assigned enzyme activity score for 28/95 (29%) and 2/93 samples (2.2%) for *CYP2D6* and *CYP2C19*, respectively (sample selection enriched for structural variants in *CYP2D6*). These changes in assigned activity score were due to both changed genotype assignments and to new genotype assignments for samples that were "no calls" on AmpliChip (Fig. 3.1). For *CYP2C19*, the highest concordance with consensus genotype was in the Luminex and PharmacoScan data (100%). Data from Luminex, Agena, TaqMan, AmpliSeq, and PharmacoScan were 100% concordant for the *CYP2C19*2* and *CYP2C19*17*, the most common

Table 3.2 A. Comparative Sanger sequencing and Luminex genotyping data for *CYP2D6* variants in samples with *CYP2D7-2D6* hybrid haplotypes

Sample	Method	31G>A	100C>T	124G>A	137_138insT	882G>C	1660G>A	1708delT	1847G>A	2550delA	2851C>T	2936A>C	2989G>A	3184G>A	4181G>C
EU093102	NA	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	WT	WT	Sequence not present	WT	MUT
GQ162807	NA	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	MUT	WT	WT	WT	MUT
1	Luminex	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	WT	WT	Low Signal	WT	MUT
	Sanger	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	WT	WT	Sequence not present	WT	MUT
3	Luminex	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	MUT	WT	WT	WT	MUT
	Sanger	MUT	WT	WT	MUT	WT	WT	WT	WT	WT	MUT	WT	WT	WT	MUT

Sample 1 aligns to EU093102, sequence for the *CYP2D6*13* haplotype previously known as *CYP2D6*66*.

Sample 3 aligns to GQ162807, sequence for the *CYP2D6*13* haplotype previously known as *CYP2D6*77* and found in a tandem arrangement with *CYP2D6*2*.

Table 3.2 B. Comparative Sanger sequencing and Luminex genotyping data for *CYP2D6* variants a sample with *CYP2D6-2D7* hybrid haplotypes

Method	-1584C>G	31G>A	100C>T	124G>A	138insT	883G>C	1023C>T	1659G>A	1707delT	1758G>T/A	1758G>T/A	1846G>A	2549delA	2850C>T	2988G>A	3183G>A
Luminex	WT	WT	MUT	WT	MUT	WT	WT	WT	WT	WT	WT	MUT	WT	WT	WT	WT
Sanger	WT	WT	MUT	WT	MUT	WT	WT	WT	WT	WT	WT	MUT	WT	WT	WT	WT

Sample aligns to EU530605 (a *CYP2D6*4.013* hybrid haplotype)

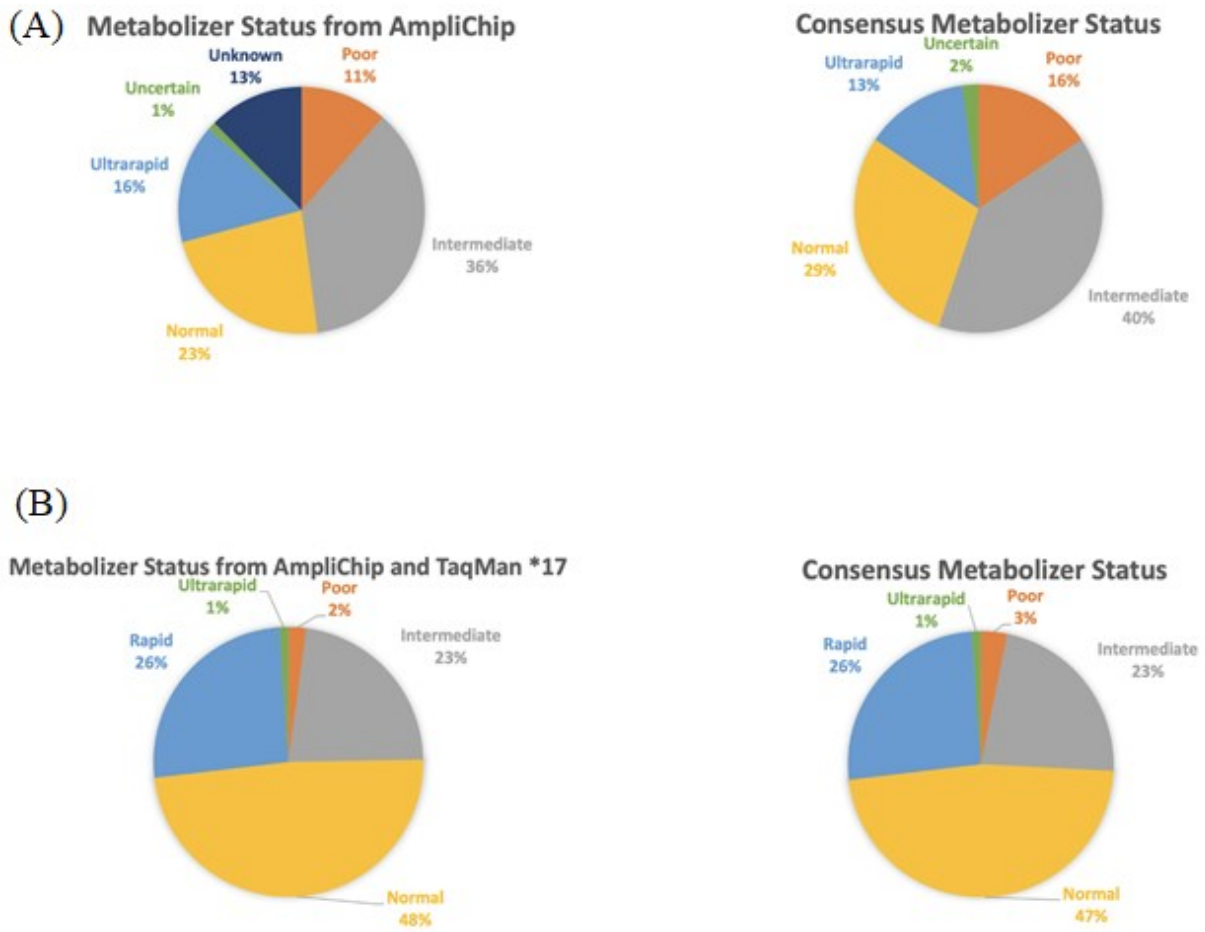

Figure 3.1 Revision in Deduced Metabolizer Status for *CYP2D6* and *CYP2C19*. (A) Change in distribution of *CYP2D6* metabolizer status deduced from genotype, from prior data to revised consensus data. (B) Change in distribution of *CYP2C19* metabolizer status deduced from genotype, from prior data to revised consensus data.

loss-of-function and gain-of- function haplotypes, respectively, in individuals of European ancestry. No adjustments in the prior AmpliChip and TaqMan data were therefore required for either of these haplotypes; prior clinical association analyses conducted on the basis of these *CYP2C19* haplotypes are therefore valid (Fabbri et al., 2018; Huezo-Diaz et al., 2012).

For *CYP2D6*, all technologies other than the AmpliChip were able to reliably detect the *CYP2D6*5*. Haplotype phasing of *CYP2D6xNs* was achieved by using relevant TaqMan assays on genomic DNA (Supplementary Fig. 1), or by genotyping an amplicon specific for the *xN*. Although using allelic ratios to cluster TaqMan genotype data leaves a degree of uncertainty

around genotypes (e.g., if only one probe amplifies, it may not be possible to distinguish between C/C, CC/C, CC/− and C/−), this technique can be used effectively to distinguish different heterozygote groups (Supplementary Fig. 1). A strength of the sample set was the availability of prior AmpliChip data including haplotype phasing of *CYP2D6xNs*. The haplotype phasing achieved with our TaqMan allelic ratio method was consistent with the prior data, where available. One sample was genotyped as having a multiplication (i.e., more copies than 2), specifically of *CYP2D6*41*, which has been previously described (Gaedigk et al., 2007; Gaedigk et al., 2012). The majority of the revisions in assigned enzyme activity score were due to the inability of AmpliChip to detect hybrids (Supplementary Table 5) and a sensitivity issue for *CYP2D6*5* detection by AmpliChip. The latter has been previously reported (Buermans et al., 2017; Henriques et al., 2020) by us and other investigators, and relates to the particular sequence used to design detection of *CYP2D6*5* by the AmpliChip.

A focus of recent research on *CYP2D6* is the hybrid haplotypes (Black et al., 2012; Gaedigk et al., 2010a; Gaedigk et al., 2010b; Kramer et al., 2009). We have developed efficient methodology for characterizing a range of hybrid haplotypes: a haplotype translation tool for the interpretation of combinations of *CYP2D6* CNV and SNV data including some hybrids and hybrid tandems (Supplementary Table 1A-C), methodology for *CYP2D6* Sanger sequencing, and adaptation of the Luminex CYP2D6 assay for amplicon sequencing with provision of concordance data for this versus Sanger sequencing to facilitate the application of other multiplex technologies to hybrid amplicons. In addition, we have developed a custom assay (ANT2NCE) that works on L-PCR amplicons for the sequence that occurs in *CYP2D6* hybrids such as *CYP2D6*36* representing a CYP2D7 exon 9 conversion. We also provide an algorithm for efficient clinical workflow that includes hybrid haplotypes including hybrid tandems (Fig.

3.2). The high degree of concordance between amplicon Luminex CYP2D6 and Sanger sequencing data is important and extends the coverage of the Luminex CYP2D6 assay to hybrids. Unfortunately, since we made this discovery, the assay has been withdrawn from the market. However, its components are still available for use as a laboratory developed test. Other multiplex assays currently available (such as the AmpliSeq Pharmacogenomics Panel, and the Agena MassARRAY Veridose Core plus CNV) could be likewise adapted. Of note, the workflow algorithm is capable of being adapted for CYP2C19, for which structural variants have been recently identified.

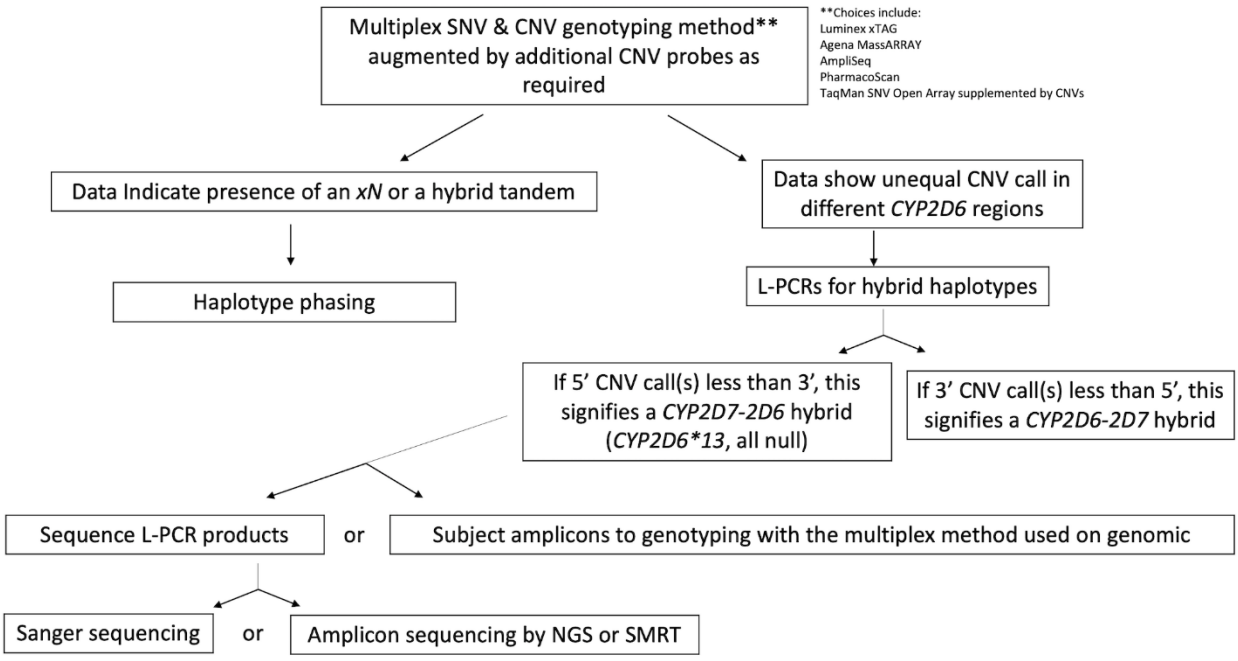

Figure 3.2 Clinical workflow algorithm for CYP2D6 genotyping.

The efficient clinical workflow algorithm for CYP2D6 genotyping provided in Fig. 3.2 includes: multiplex SNV and CNV assays, haplotype phasing, and L-PCRs with multiplex genotyping or sequencing (Fig. 3.2). Appropriate positive controls (e.g., from the GeT-RM (GeT-RM, 2019), especially for the haplotypes that we did not see in this European sample set and which might be found in other ethnic groups, should be run with the assays. We

have provided cross-validation data between a multiplex assay and Sanger sequencing for amplicons from *CYP2D6*4.013* haplotype and *CYP2D6*13* haplotypes (Table 3.2 A, B). These can act as reference data for other multiplex assays processing hybrid amplicons. Laboratories desiring to use this workflow could use one of the technologies offering multiplex SNV and CNV data (e.g., the Open Array could be supplemented by TaqMan CNV assays) on genomic DNA, with the resultant data suggesting samples with hybrid alleles; these samples would require L-PCR amplicon generation and subsequent testing using the same multiplex assay as used on the genomic DNA (adapted as necessary). Factors influencing choice of technology by a particular laboratory may include: its local availability, relevant expertise, cost, minimum and maximum number of samples per run, any required data interpretation including bioinformatics, and turnaround time. Laboratories needing to process a small number of samples rapidly (e.g., for clinicians in acute care settings) could select an assay with a low minimum number of samples per run (e.g., Luminex). Others needing to process a large number of samples rapidly could choose a large maximum number of samples per run, such as NGS or array options. The technologies have other strengths and weaknesses, e.g., in regard to their coverage of *CYP2D6* CNVs. The Ion AmpliSeq Pharmacogenomics Panel provides the greatest number of regions that may be used for *CYP2D6* CNV derivation; PharmacoScan provides 5′ and 3′ UTR CNV probes; and TaqMan provides CNV assays for intron 2, intron 6, and exon 9. A TaqMan CNV assay for the 5′ UTR is also available (Hs07545275_cn) (Fukunaga et al., 2021).

To increase the breadth of *CYP2D6* coverage to haplotypes in Tiers 1 and 2 of the recommendations by Pratt et al. (2021) we developed custom TaqMan assays: ANCFHM6 for rs61736512, which is part of the defining variant in *CYP2D6*29*, and ANWRUE2 for rs72549356 in *CYP2D6*40*. In regard to other haplotypes listed herein, although *CYP2D6*39* is

of normal function (Hongkaew et al., 2021; Shimada et al., 2001), the enzyme activity for individuals of this haplotype in diverse ancestral populations is as yet unknown. Therefore, arguably, it can be justified to cover this haplotype in clinical genotyping. One of our samples, with a consensus *CYP2D6* genotype of **10/*41* had an alternative genotype of *CYP2D6*39.001/*69*. The list of haplotypes covered by assays reported herein also includes haplotypes of known function but to date without reference samples (*CYP2D6*12* and *CYP2D6*69*) (Gaedigk et al., 2009; Gaedigk et al., 2017; Marez et al., 1996; Pratt et al., 2021). Should these be identified in clinical genotyping and confirmed using a second method, then reference samples could be made available to other research and clinical labs. The rationale for inclusion of *CYP2D6*70* ((Matimba et al., 2009); rated as uncertain in function, with a moderate evidence level by PharmVar) and *CYP2D6*107* (Qiao et al., 2016); rated as unknown function, limited evidence level (PharmVar, 2021c) is less strong. We suggest including them on a research basis to maximize potential utility gaining knowledge relevant to clinical testing in diverse populations. When we used a *CYP2D6* translator with the **107* included, this resulted in several alternative calls in which a **1* was substituted by a **107*.

In regard to *CYP2C19*, the recommendation of (Pratt et al., 2018) covers *CYP2C19* change-of-function haplotypes of ≥1% in any ethnic group (PharmGKB, 2021a), which include *CYP2C19*2-*10, *17*, and **35*). We also suggest an additional TaqMan assay (C_312628039_10) for the c.463G>T variant (rs374036992) that may be found on the *CYP2C19*17* haplotype and introduces a premature stop codon (Skierka et al., 2014), and an assay to enable *CYP2C19*17* haplotype phasing (Skierka et al., 2014).

We acknowledge several limitations of this work. Firstly, we have not covered rare variants. It has been estimated that ~6.3% of the variance in olanzapine concentration is

accounted for by rare *CYP2D6* variants, while rare variants are estimated to account for 4.4% of the overall genetic variability of *CYP2C19* function (Ingelman-Sundberg et al., 2018). Such variants would be identifiable by using methods that we have not validated, such as SMRT. While there are some papers reporting the use of SMRT to identify *CYP2D6* variants (Buermans et al., 2017; Fukunaga et al., 2021; van der Lee et al., 2021), SMRT has however, not yet been validated on as broad a range of hybrid configurations as were included in the present report.

Secondly, the work was conducted in a set of samples from European individuals being treated for depression, with samples being selected as being representative for genotypes available in the whole set and with enrichment for *CYP2D6* structural variants. As such, we did not find *CYP2D6* haplotypes that would be more commonly found in other ethnic groups, such as **29*. Therefore, although the technologies are theoretically able to identify this haplotype, our lack of detection prevented confirmation. Of note, there are reference samples for test validation available with this haplotype from the Genetic Testing Reference Material Program (GeT-RM, 2019). Thirdly, theoretically it is possible that our CNV detection methods resulted in false positive calls for copy number loss in introns 2 and 6, owing to sequence variation in the relevant regions (Turner et al., 2021). However, as we used three different technologies (AmpliSeq, Pharmacoscan, and TaqMan), covering probes in multiple regions of CYP2D6 in addition to introns 2 and 6, and subjected any putative hybrid haplotypes to L-PCR and Sanger sequencing, we do not think this is a significant concern.

In summary, this study provides cross-validation data on a range of *CYP2D6* and *CYP2C19* genotypes including *CYP2D6* hybrids and hybrid tandems for several assays including: AmpliChip CYP450, TaqMan CNV and SNV assays, xTAGv3 Luminex CYP2D6

and CYP2C19, the Agena CYP2C19 content from the Veridose Core, PharmacoScan, and the Ion AmpliSeq Pharmacogenomics Panel. In addition, we provide the first reference data for multiplex assay amplicon genotyping for some *CYP2D6* hybrid haplotypes using long-range polymerase chain reactions (L-PCRs) followed by Sanger sequencing and Luminex. We have also developed a broader range of TaqMan SNV assays, and haplotype phasing methodology with TaqMan that is adaptable for other technologies. Finally, we have established a multiplex genotyping method for efficient identification of some hybrid haplotypes and created a customizable automated translator of SNV and CNV data for haplotype assignment. Together this work has laid the foundation for an efficient clinical workflow algorithm.

3.6 Acknowledgments

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3.7 Supplementary Material

Table S1A Sequencing primers for the *CYP2D7-2D6* and *CYP2D6-2D7* (*CYP2D6*13*) hybrid haplotypes.

Hybrid	Primer Name	Primer Sequence	Reference
2D7-2D6	5000F	GTCGTCCAAGGTTCAAATAGG	Gaedigk, personal communication
2D7-2D6	8192R	CCCTGCAAGACTCCACGG	Gaedigk, personal communication
2D7-2D6	E1F	CAGCTCCCTTTATAAGGGAAGGGT	Hosono et al., 2009
2D7-2D6	4728F	CGAAATCGAGGATGAAGG	Gaedigk, personal communication
2D7-2D6	Universal fragment A reverse primer	CGACTGAGCCCTGGGAGGTAGGTA	Gaedigk et al., 2015
2D7-2D6	5041R	TTGTCAAGCCAGGATCAC	Gaedigk, personal communication
2D7-2D6	5681F	GCCCTGTGACCAGCTGGACAGAGCC	Gaedigk, personal communication
2D7-2D6	8615R	GGCAAGGGTAACTGACATCTG	Gaedigk, personal communication
2D7-2D6	5986R	GCCTTCCCAGTTCCCGC	Gaedigk, personal communication
2D7-2D6	6383R	CACGACCATGTCTGAGATGTCC	Gaedigk, personal communication
2D7-2D6	6944R	CACCTGTCAGCCCAGATGC	Gaedigk, personal communication
2D7-2D6	7511R	CCCTGTACTTCGATGTCAC	Gaedigk, personal communication
2D7-2D6	FE2	GGCCCTGACCCTCCCTCTGC	Broly et al., 1995
2D7-2D6	FE3	TGCCCGTCCCACCCCC	Broly et al., 1995
2D7-2D6	FE4	CCCGCATCTCCCACCCCC	Broly et al., 1995
2D7-2D6	FE5	GACCCCGTTCTGTCTGGTGT	Broly et al., 1995
2D7-2D6	FE6	GTATGCTCTCGGCCCTGCTC	Broly et al., 1995
2D7-2D6	FE7	GTGGGGACGCATGTCTGTCC	Broly et al., 1995
2D7-2D6	FE8	TCACCCTGCATCTCCTGCCC	Broly et al., 1995
2D7-2D6	RE3	GCCCTTCTGCCCATCACCC	Broly et al., 1995

Table S1B Sequencing primers for the *CYP2D7-2D6* and *CYP2D6-2D7* (*CYP2D6*68*) hybrid haplotypes.

Hybrid	Primer Name	Primer Sequence	Reference
2D6-2D7 (*68)	2D6-Universal-D-F	CCAGAAGGCTTTGCAGGCTTCAG	Gaedigk et al., 2015
2D6-2D7 (*68)	-1108R	GACCACTCCTGTCCAGAGG	*
2D6-2D7 (*68)	Prealpha F	TCACCCCCAGCGGACTTATCA	Kramer et al., 2009
2D6-2D7 (*68)	1163F	CTCATGCCTATAATCCCAGC	Gaedigk, personal communication
2D6-2D7 (*68)	2908R	TGGCTCCCCTCCATTGTGC	Gaedigk, personal communication
2D6-2D7 (*68)	3131F	GGATCCTCCATAACGTTCCCACC	Gaedigk, personal communication
2D6-2D7 (*68)	3526F	TGTAATCGTGTCCCTGCAAG	Gaedigk, personal communication
2D6-2D7 (*68)	3922R	CCTGGTCGGAGAAGTCACC	Gaedigk, personal communication
2D6-2D7 (*68)	4628R	CAATGGGCTTGAATTCCCACTGCCAAG	Gaedigk, personal communication
2D6-2D7 (*68)	4728F	CGAAATCGAGGATGAAGG	Gaedigk, personal communication
2D6-2D7 (*68)	5041R	TTGTCAAGCCAGGATCAC	Gaedigk, personal communication
2D6-2D7 (*68)	-342F	TATGAGCCTAGCTGGGAGGT	*
2D6-2D7 (*68)	FE2	GGCCCTGACCCTCCCTCTGC	Broly et al., 1995
2D6-2D7 (*68)	FE4	CCCGCATCTCCCACCCCC	Broly et al., 1995
2D6-2D7 (*68)	FE5	GACCCCGTTCTGTCTGGTGT	Broly et al., 1995
2D6-2D7 (*68)	403F	CCAAAGGCCAAGGAAGAGTA	*
2D6-2D7 (*68)	1939F	AACGGTCTCTTGGACAAAGC	*
2D6-2D7 (*68)	P1	TCCCCCACTGACCCAACTCT	Gaedigk, personal communication
2D6-2D7 (*68)	RE2	CTCTGTCCCCACCGCTGCTT	Broly et al., 1995
2D6-2D7 (*68)	RE3	GCCCTTCTGCCCATCACCC	Broly et al., 1995
2D6-2D7 (*68)	RE5	CCGTGGCAGCCACTCTC	Broly et al., 1995
2D6-2D7 (*68)	139R	GTTAGCATCCCATTCCCAGA	*
2D6-2D7 (*68)	1819R	AGAGTCCTTGGCCTCTCCTG	*

An asterisk denotes a novel primer, with the numbering being according to the ATG start on NG_008376.4 (LRG_303).

Table S1C Sequencing primers for the *CYP2D7-2D6* and *CYP2D6-2D7* (*CYP2D6*4.013*) hybrid haplotypes

Hybrid	Primer Name	Primer Sequence	Reference
2D6-2D7 (*4.013)	1163F	CTCATGCCTATAATCCCAGC	Gaedigk, personal communication
2D6-2D7 (*4.013)	2908R	TGGCTCCCCTCCATTGTGC	Gaedigk, personal communication
2D6-2D7 (*4.013)	4628R	CAATGGGCTTGAATTCCCACTGCCAAG	Gaedigk, personal communication
2D6-2D7 (*4.013)	Universal fragment D forward primer	CCAGAAGGCTTTGCAGGCTTCAG	Gaedigk et al., 2015
2D6-2D7 (*4.013)	Prealpha F	TCACCCCCAGCGGACTTATCA	Kramer et al., 2009
2D6-2D7 (*4.013)	P1	TCCCCCACTGACCCAACTCT	Sachse et al., 1997
2D6-2D7 (*4.013)		CCTGGTCGGAGAAGTCACC	Gaedigk, personal communication
2D6-2D7 (*4.013)	3131F	GGATCCTCCATAACGTTCCCACC	Gaedigk, personal communication
2D6-2D7 (*4.013)	3526F	TGTAATCGTGTCCCTGCAAG	Gaedigk, personal communication
2D6-2D7 (*4.013)	4728F	CGAAATCGAGGATGAAGG	Gaedigk, personal communication
2D6-2D7 (*4.013)	FE6	GTATGCTCTCGGCCCTGCTC	Broly et al., 1995
2D6-2D7 (*4.013)	FE7	GTGGGGACGCATGTCTGTCC	Broly et al., 1995
2D6-2D7 (*4.013)	RE3	GCCCTTCTGCCCATCACCC	Broly et al., 1995
2D6-2D7 (*4.013)	RE4	CCTCGGTCTCTCGCTCCGC	Broly et al., 1995
2D6-2D7 (*4.013)	RE5	CCGTGGCAGCCACTCTC	Broly et al., 1995
2D6-2D7 (*4.013)	RE6	ACTGTTTCCCAGATGGGCTC	Broly et al., 1995
2D6-2D7 (*4.013)	FE2	GGCCCTGACCCTCCCTCTGC	Broly et al., 1995
2D6-2D7 (*4.013)	8615R	GGCAAGGGTAACTGACATCTG	Gaedigk, personal communication
2D6-2D7 (*4.013)	RE2	CTCTGTCCCCACCGCTGCTT	Broly et al., 1995
2D6-2D7 (*4.013)	FE8	TCACCCTGCATCTCCTGCCC	Broly et al., 1995
2D6-2D7 (*4.013)	FE3	TGCCCGTCCCACCCCC	Broly et al., 1995
2D6-2D7 (*4.013)	4369F	GTTGGGATCATCCTCCTCAG	*
2D6-2D7 (*4.013)	-1360F	AAAAGCTAGACGTGGTGGCA	*
2D6-2D7 (*4.013)	-1108R	GACCACTCCTGTCCAGAGG	*
2D6-2D7 (*4.013)	8004F	CGACACTCATCACCAACCTGT	Gaedigk, personal communication
2D6-2D7 (*4.013)	8192R	CCCTGCAAGACTCCACGG	Gaedigk, personal communication
2D6-2D7 (*4.013)	-342F	TATGAGCCTAGCTGGGAGGT	*
2D6-2D7 (*4.013)	403F	CCAAAGGCCAAGGAAGAGTA	*
2D6-2D7 (*4.013)	1939F	AACGGTCTCTTGGACAAAGC	*
2D6-2D7 (*4.013)	2979F	GCCTCCTGCTCATGATCCTA	*
2D6-2D7 (*4.013)	3502F	ACCTAGTCCTCAATGCCACC	*
2D6-2D7 (*4.013)	139R	GTTAGCATCCCATTCCCAGA	*
2D6-2D7 (*4.013)	1819R	AGAGTCCTTGGCCTCTCCTG	*
2D6-2D7 (*4.013)	2715R	GGGATGTCATATGGGTCACA	*
2D6-2D7 (*4.013)	3588R	ACGGAAGGGGACAGGGAG	*

An asterisk denotes a novel primer, with the numbering being according to the ATG start on NG_008376.4 (LRG_303).

Table S2 Comparative *CYP2D6* data for samples with copy number data indicating one copy of the gene, providing consensus genotype, and previous and new predicted enzyme phenotypes

TaqMan CNV data			PScan CNV data			IonS5	IonS5	AmpliChip	Luminex (genomic) RUO	PScan	Ion S5	Consensus genotype	Activity Score Consensus	Previous Phenotype	New Phenotype
I2	I 6	E9	5'	E9	3'	gene	E9								
1	1	1	1	1	1	1	1	*4xN/*5	*4/*5	*4/*5	*4/*5	*4/*5	0	PM	PM
1	1	1	1	1	1	1	1	*5/*35	*5/*35	*5/*35	*5/*35	*5/*35	1	NM	IM
1	1	1	1	1	1	1	1	*2/*2	*2/*5	*2/*5	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020, *2.021/*5	*2/*5	1	NM	IM
1	1	1	1	1	1	1	1	*5/*10	*5/*10	*5/*10	*5/*10	*5/*10	0.25	IM	IM
1	1	1	1	1	1	1	1	*1/*4	*1/*5	*1/*5	*1/*5	*1/*5	1	NM	IM
1	1	1	1	1	1	1	1	*5/*41	*5/*41	*5/*41	*5/*41	*5/*41	0.5	IM	IM
1	1	1	1	1	1	1	1	*1/*2xN	*1/*5	*1/*5	*1/*5	*1/*5	1	UM	IM
1	1	1	1	1	1	1	1	*2/*4	*2/*5	*2/*5	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020, *2.021/*5	*2/*5	1	NM	IM
1	1	1	1	1	1	1	1	*3/*5	*3/*5	*3.001/*5	*3/*5	*3/*5	0	PM	PM
1	1	1	1	1	1	1	1	*5/*35	*5/*35	*5/*35	*5/*35	*5/*35	1	NM	IM
1	1	1	1	1	1	1	1	*4/*35	*3/*5	*3.001/*5	*3/*5	*3/*5	0	NM	PM
1	1	1	1	1	1	1	1	*5/*41	*5/*41	*5/*41	*5/*41	*5/*41	0.5	IM	IM
1	1	1						*4/*5	*4/*5		NA	*4/*5	0		

PScan = PharmacoScan, I2 = intron 2, I6 = intron 6, E9 = exon 9, 5' = 5' flanking region, 3' = 3' flanking region

Bold font denotes adjustments in data owing to new genotypic data.

Blue font denotes adjustments in data owing to revised phenotypic definitions based on activity score (Caudle et al., 2020).

Table S3 Data for samples with at least one extra *CYP2D6* gene (i.e., a duplication, or in the case of the sample of consensus genotype *CYP2D6*41x3/*3*, a multiplication, specifically, a triplication). Haplotype phasing was achieved by TaqMan genotyping of genomic DNA and/or of an amplicon specific for duplicated *CYP2D6* gene (using primers as described by Gaedigk et al., 2007.).

TaqMan CNV data			PScan CNV data			IonS5	IonS5	AmpliChip	PScan	IonS5	Luminex (genomic) RUO	TaqMan *2 (genomic)	TaqMan *4 (genomic)	TaqMan *4 (amplicon)	TaqMan *3 (genomic)	TaqMan *6 (genomic)	Taqman *35 (genomic)	TaqMan *41 (genomic)	*Consensus Genotype*	Activity Score Consensu
												rs16947	rs3892097	rs3892097			rs769258	rs28371725		
I2	I6	E9	5'	E9	3'	Gene	E9													
3	3	3	3	3	3	3	3	*1xN/*4	*/*1/*4jxN	*1/*4x2, *1.011/*4.002x2, *1x2/*4	(*1/*4); DUP	GG/G	CC/T	C	TT/T	NA	NA	CC/C	*1x2/*4	2
3	3	3	3	3	3	3	3	*1xN/*2	*/*1/*2jxN	*1/*2.001x2, *1x2/*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021	(*1/*2); DUP	GG/A	NA	C	TT/T	NA	CC/C	CC/C	*1x2/*2	3
3	3	3	3	3	3	3	3	*1/*2xN	*/*1/*2jxN	*1/*2.001x2, *1x2/*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021	(*1/*2); DUP	AA/G	CC/C	C	TT/T	NA	CC/C	CC/C	*2x2/*1	3
3	3	3	3	3	3	3	3	*1xN/*2	*/*1/*2jxN	*1/*2.001x2, *1x2/*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021	(*1/*2); DUP	GG/A	NA	C	TT/T	NA	CC/C	CC/C	*1x2/*2	3
3	3	3	3	3	3	3	3	*2xN/*4	*/*2/*4jxN	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*4x2, *2.001x2/*4	(*2/*4); DUP	AA/G	NA	C	TT/T	NA	CC/C	CC/C	*2x2/*4	2
3	3	3	3	3	3	3	3	no data	(*2/*4)xN	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*4x2, *2.001x2/*4	(*2/*4); DUP	AA/G	CC/T	NA	NA	NA	NA	CC/C	*2x2/*4	2
3	3	3	2	3	3	3	3	*2xN/*4	*/*2/*4jxN	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*2.001x2	(*2/*4); DUP	AA/A	CC/C	NA	NA	NA	NA	CC/C	*2x2/*4	2
3	3	3	3	2	3	3	3	*2/*2xN	*2/*2	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*2.001x2	(*2/*2); DUP	AA/A	CC/C	NA	NA	NA	NA	CC/C	*2x2/*2	3
3	3	3	3	3	3	3	3	*2/*2xN	*2/*2	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*2.001x2	(*2/*2); DUP	AA/A	CC/C	NA	NA	NA	NA	CC/C	*2x2/*2	3
3	3	3	3	3	3	3	3	*2xN/*41	*2/*2xN	*2/*2.001X2, *2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*2x2	(*2/*2); DUP	AA/A	NA	C	TT/T	NA	NA	CC/C	*2x2/*2	3
3	3	3	3	3	3	3	3	*1/*4xN	(*1/*4)xN	*1/*4x2, *1.011/*4.002x2, *1x2/*4	(*1/*4); DUP	GG/G	TT/C	T	TT/T	NA	NA	CC/C	*4x2/*1	1
3	3	3	3	3	3	UND		*1xN/*6	(*1/*6)xN	/*1/*6x2, *1x2/*6]	(*1/*6); DUP	GG/G	CC/C	NA	NA	AA/-	NA	CC/C	*1x2/*6	2
3	3	3	3	3	3	2	3	*1/*1xN	*1/*1xN	/*1/*1, *1/*61, *1x2/*5,...]	(*1/*1); DUP	GG/G	NA	NA	TT/T	NA	CC/C	CC/C	*1x2/*1	3
3	3	3	3	3	3	2	3	*1/*1xN	*1/*1xN	/*1/*1, *1/*61, *1x2/*5,...]	(*1/*1); DUP	GG/G	NA	C	TT/T	NA	NA	CC/C	*1x2/*1	3
3	3	3	3	3	3	2	3	*1xN/*2	(*1/*2)xN	/*1/*63, *61/*63]	(*1/*2); DUP	GG/A	NA	C	TT/T	NA	CC/C	CC/C	*1x2/*2	3
3	3	3	3	3	3	2	3	*2/*4xN	(*2/*4)xN	/*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*4, *2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*4.013]	(*2/*4); DUP	GG/A	TT/C	NA	NA	NA	NA	CC/C	*4x2/*2	1
3	3	3	3	3	3	2	3	*1xN/*4	(*1/*4)xN	no translation available	(*1/*4); DUP	GG/G	CC/T	C	TT/T	NA	NA	CC/C	*1x2/*4	2
3	3	2	3	3	3	3	3	*1xN/*2	(*1/*35)xN	*/*35x2, *1x2/*35	(*1/*35); DUP	GG/A	NA	C	TT/T	NA	CC/T	CC/C	*1x2/*35	3
failed	3	3	3	3	3	2	3	*1/*1xN	*/*1xN	no translation available	(*1/*1); DUP	GG/G	CC/C	C	TT/T	NA	CC/C	CC/C	*1x2/*1	3
4	4	4	3	3	3	3	3	*3/*41xN	(*1/*41)xN,(*	no translation available	(*3/*41); DUP	AAA/G or AA/G	NA	C	TT/- or TTT/-	NA	NA	TTT/C or TT/C	*41x3/*3	1.5
3	3	3	3	3	3	2	3	no data	(*1/*4)xN	no translation available	(*1/*4); DUP	GG/G	TT/C	T	TT/T	NA	CC/C	CC/C	*4x2/*1	1
3	3	3	3	3	3	2	3	*2xN/*35	(*2/*35)xN	no translation available	(*2/*35); DUP	AA/A	CC/C	C	TT/T	NA	CC/T	CC/C	*2x2/*35	3
3	3	3	3	3	3	2	3	*/*41xN	(*1/*2)xN	no translation available	(*1/*2); DUP	AA/G	CC/C	NA	NA	NA	CC/C	CC/C	*2x2/*1	3

Table S4 Comparative *CYP2D6* data for samples with a CNV call of 2.

TaqMan CNV data			PharmacoScan 2D6 CNV data			IonS5 Cn	IonS5 Cn	PharmacoScan r8.2	AmpliChip	IonS5	Luminex (genomic) RUO	TaqMan *2 SNP_Genomic	TaqMan *4 SNP_Genomic	TaqMan *6 SNP_Genomic	Taqman *3 SNP_Genomic	Taqman *35 SNP_Genomic	Taqman *41 SNP_Genomic	consensus genotype	Activity Score Consensus
I2	I 6	E9	5'	E9	3'	gene	E9					rs16947	rs3892097		rs35742686	rs76925S	rs28371725		
2	2	2	2	2	2	2	2	*4/*41	*4/*41B	*4/*41	*4/*41	A/G	T/C	A/A	T/T	C/C	C/T	*4/*41	0.5
2	2	2	2	2	2	2	2	*9/*35	*9/*35	*9/*35	*9/*35	A/G	C/C	A/A	T/T	C/T	C/C	*9/*35	1.5
2	2	2	2	2	2	2	2	*1/*9	*1/*9	*1/*9	*1/*9	G/G	C/C	A/A	T/T	C/C	C/C	*1/*9	1.5
2	2	2	2	2	2	2	2	*3.001/*41	*3/*41	*3/*41	*3/*41	A/G	C/C	A/A	T/-	C/C	C/T	*3/*41	0.5
2	2	2	2	2	2	2	2	*4/*41	*4/*41	*4/*41	*4/*41	A/G	T/C	A/A	T/T	C/C	C/T	*4/*41	0.5
2	2	2	2	2	2	2	2	*35/*35	*35/*35	*5/*35X2, *35/*35	*35/*35	A/A	C/C	A/A	T/T	T/T	C/C	*35/*35	2
2	2	2	2	2	2	2	2	*6/*41	*6/*41	*6/*41	*6/*41	A/G	C/C	A/-	T/T	C/C	C/T	*6/*41	0.5
2	2	2	2	2	2	2	2	*1/*41	NA	no translation available	*1/*41	A/G	C/C	A/A	T/T	C/C	C/T	*1/*41	1.5
2	2	2	2	2	2	2	2	*2/*9	*2/*9	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*9	*2/*9	A/G	C/C	A/A	T/T	C/C	C/C	*2/*9	1.5
2	2	2	2	2	2	2	2	*3.001/*9	*3/*9	*3/*9	*3/*9	G/G	C/C	A/A	T/-	C/C	C/C	*3/*9	0.5
2	2	2	2	2	2	2	2	*2/*3.001	*2/*3	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*3	*2/*3	A/G	C/C	A/A	T/-	C/C	C/C	*2/*3	1
2	2	2	2	2	2	2	2	*6/*10	*6/*10	*6/*10	*6/*10	G/G	C/C	A/-	T/T	C/C	C/C	*6/*10	0.25
2	2	2	2	2	2	2	2	*1/*17	*1/*17	*1/*17	*1/*17	A/G	C/C	A/A	T/T	C/C	C/C	*1/*17	1.5
2	2	2	2	2	2	2	2	*9/*15	*9/*15	*9/*15	*9/*15	G/G	C/C	A/A	T/T	C/C	C/C	*9/*15	0.5
2	2	2	2	2	2	2	2	*9/*41	*9/*41	*9/*41	*9/*41	A/G	C/C	A/A	T/T	C/C	C/T	*9/*41	1
2	2	2	2	2	2	2	2	*10/*35	*10/*35	*10/*35	*10/*35	A/G	C/C	A/A	T/T	C/T	C/C	*10/*35	1.25
2	2	2	2	2	2	2	2	*35/*41	*35/*41	*35/*41	*35/*41	A/A	C/C	A/A	T/T	C/T	C/T	*35/*41	1.5
2	2	2	2	2	2	2	2	*41/*41	*41/*41	*41/*41	*41/*41	A/A	C/C	A/A	T/T	C/C	T/T	*41/*41	1
2	2	2	2	2	2	2	2	*4/*6	*4/*6	*4/*6	*4/*6	G/G	T/C	A/-	T/T	C/C	C/C	*4/*6	0
2	2	2	2	2	2	2	2	*1/*1	*1/*7	*1/*1, *1X2/*5	*1/*1	G/G	C/C	A/A	T/T	C/C	C/C	*1/*1	2
2	2	2	2	2	2	2	2	*4/*35	*4/*35	*4/*35	*4/*35	A/G	C/T	A/A	T/T	C/T	C/C	*4/*35	1
2	2	2	2	2	2	2	2	*10/*41	*10/*41	*10/*41	*10/*41	A/G	C/C	A/A	T/T	C/C	C/T	*10/*41	0.75
2	2	2	2	2	2	2	2	*2/*41	*2/*35xN	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*41	*2/*41	A/A	C/C	A/A	T/T	C/C	C/T	*2/*41	1.5
2	2	2	2	2	2	2	2	*1/*1	*1xN/*5	{*1/*1, *1/*61, *1X2/*5,...}	{*1/*5}; DUP	GG/-	CC/-	AA/-	TT/-	CC/-	CC/-	*1xN/*5	2
2	2	2	2	2	2	2	2	*6/*22	*1/*6	*1/*6	*1/*6	G/G	C/C	A/-	T/T	C/C	C/C	*1/*6 or *22/*6	1
2	2	2	2	2	2	2	2	*2/*6	*2/*6	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*6	*2/*6	A/G	C/C	A/-	T/T	C/C	C/C	*2/*6	1
2	2	2	2	2	2	2	2	UND	*1/*1	*15/*35	{*1/*1, *1/*61, *1X2/*5,...}	*1/*1	G/G	C/C	A/A	T/T	C/C	*1/*1	2
2	2	2	2	2	2	2	2	*10/*10	*10/*10	*5/*10X2, *10/*10	*10/*10	G/G	C/C	A/A	T/T	C/C	C/C	*10/*10	0.5
2	2	2	2	2	2	UND	UND	*4/*7	*4/*7	no translation available	*4/*7	G/G	C/T	A/A	T/T	C/C	C/C	*4/*7	0
2	2	2	2	2	2	2	2	*6/*35	*6/*35	*6/*35	*6/*35	A/G	C/C	A/-	T/T	C/T	C/C	*6/*35	1
2	2	2	2	2	2	2	2	*4/*41	*7/*41	*4/*41	*4/*41	A/G	C/T	A/A	T/T	C/C	C/T	*4/*41	0.5
2	2	2	2	2	2	2	2	*17/*41	*17/*41	*17/*41	*17/*41	A/G	C/C	A/A	T/T	C/C	C/T	*17/*41	1
2	2	2	2	2	2	2	2	*1/*25	*1/*25	*1/*1, *1X2/*5	*1/*1	G/G	C/C	A/A	T/T	C/C	C/C	*1/*25	uncertain (*25) [at least 1]
2	2	2	2	2	2	2	2	*2/*41	*2/*10	*2.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021/*41	*2/*41	A/A	C/C	A/A	T/T	C/C	C/T	*2/*41	1.5
2	2	2	2	2	2	2	2	*3.001/*6	*3/*6	*3/*6	*3/*6	G/G	C/C	A/-	T/-	C/C	C/C	*3/*6	0
failed	3	failed	2	2	2	2	2	*1/*41	*1/*41	*1/*41	*1/*41	A/G	C/C	A/A	T/T	C/C	C/T	*1/*41	1.5
1	2	2	2	2	2	2	2	*1/*52	*1/*52	*1/*52.001, *2.005, *2.012, *2.013, *2.018, *2.020 ,*2.021	*1/*52	G/A	C/C	A/A	T/T	C/C	C/C	*1/*52	2
2	2	2	2	2	2	3	2	*1/*3.001	*1/*3	no translation available	*1/*3	G/G	C/A	A/A	T/-	C/C	C/C	*1/*3	1
NA	2	2	2	2	2	2	2	*1/*4	NA	*1/*4, *1.011/*4.002	*1/*4	G/G	T/C	A/A	T/T	C/C	C/C	*1/*4	1
2	2	2	NA	NA	NA	NA	NA	NA	*2/*7	NA	*2/*7	G/A	C/C	A/A	T/T	C/C	C/C	*2/*7	1
2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	*35/*41	A/A	C/C	A/A	T/T	C/T	C/T	*35/*41	1.5

Table S5 Data including consensus genotypes for the samples with *CYP2D7-2D6* or *CYP2D6-2D7* hybrid genes or hybrid tandems.

AmpliChip	PScan v8.2 (20200221 translator)	PScan 2D6 CNV data			TaqMan CNV			IonS5 Call		IonS5	XL-PCR amplicon	Potential hybrid or hybrid tandem	TaqMan *2 genomic calls rs16947	TaqMan *4 genomic calls rs3892097	TaqMan 100C>T genomic calls rs1065852 (found in *10, and most *4s)	TaqMan *35 genomic calls rs769258	Consensus Genotype	Activity Score Consensus
		5pFlank	exon9	3pFlank	I2	I6	E9	2D6 Probe	E9 Probe (automatic call in brackets)									
*4/*4	*no call*	2	2	2	1	1	2	2	1	2 *no call*		E CYP2D7-2D6	G/-	T/-	A/G	C/-	*13+*4/*35	0
*4/*4	*4/*4	2	2	2	1	1	2	2	1	2 *no call*		G CYP2D7-2D6	G/G	N/A	N/A	C/-	*13/*4.013	0
*1/*1	*no call*	1	2	2	1	1	2	2	1	2 *no call*		G CYP2D7-2D6	G/G	C/C	G/G	C/-	*13/*1	1
*1/*1	*no call*	1	2	2	1	1	2	2	1	2 *no call*		G CYP2D7-2D6	G/G	C/C	G/G	C/-	*13/*1	1
*1/*2xN	*1/*2	2	3	3	3*	1	3	2	1	3 *no call*		G CYP2D7-2D6 +2D6	AA/G	C/C	GG/G	C-/C	*13+*2/*1	2
no call	*1/*2	2	3	3	3*	1	3	2	1	3 *no call*		G CYP2D7-2D6 +2D6	A/A/G	C/C	G/G/G	C-/C	*13+*2/*1	2
no call	*1/*2	2	3	3	3*	1	3	2	1	3 *no call*		G CYP2D7-2D6 +2D6	A/A/G	C/C	G/G/G	C-/C	*13+*2/*1	2
*2/*41xN	*2/*41	2	3	3	3	1	3	2	UND	*2.002, *2.005, *2.012, *2.013, *2.018, *2.020, *2.021/*41		G CYP2D7-2D6 +2D6	A/A/A	C/C	N/A	C/C	*13+*2/*41	1.5
*4/*4	*4/*4	1	2	2	1	1	2	1	2	*4.002/*4.013+*4, *4.013/*4.002x2		E CYP2D6-2D7 +2D6	G/G/G	T/T	A/A/A	C/C/C	*4.013+*4/4.002	0
*4/*35	*4/*35	1	2	2	1	1	2	2	2	*4/*35		E CYP2D6-2D7 +2D6	GG/A	T/C	A/A/G	C/T	*4.013+*4/*35	1
*1/*4	*1/*4	1	2	2	1	1	2	2	2	*1/*4, *1.011/*4.002		E CYP2D6-2D7 +2D6	G/G/G	T/C	A/A/G	C/C/C	*4.013+*4/*1	1
*1/*4	*1/*4	1	2	2	1	1	2	2	2	*1/*4, *1.011/*4.002		E CYP2D6-2D7 +2D6	G/G/G	T/C	A/A/G	C/C/C	*4.013+*4/*1	1
*4/*4	*4/*4	1	2	2	1	1	2	2	2	2 (UND) *4/*4x2, *4/*4.013+*4, *4/*4.013x2,...]		E CYP2D6-2D7 +2D6	G/G/G	T/T	A/A/A	C/C/C	*4.013+*4/*4	0
*4/*4	*4/*4	1	2	2	1	1	2	2	2	2 (UND) [*4/*4, *4/*4.013, *4.013/*4.013,...]		E CYP2D6-2D7 +2D6	G/G/G	T/T	A/A/A	C/C/C	*4.013+*4/*4	0
*2/*4	*2/*4	1	2	2	1	1	2	N/A	*no sufficient SNP data*	N/A		E CYP2D6-2D7 +2D6	G/G/A	T/C	A/A/G	C/C/C	*4.013+*4/*2	1
*no call	*10/*35	1	2	2	1	1	2	2	2	*10/*35		E CYP2D6-2D7 +2D6	G/G/A	C/C	A/A/G	C/C/T	*16+*10/*35	1.25
*4/*10	*4/*10	1	2	2	2	2	2	2	2	*4/*10		E CYP2D6-2D7 +2D6	G/-/G	T/-C	A/A/A	C/C/C	*68+*4/*10	0.25
*no call	*2/*10	2	3	3	3	3	3	3	3	(UND) [*2.001, *2.003, *2.012, *2.013, *2.018, *2.020, *2.021/*10, *2.001, *2.003, *2.012, *2.013, *2.018, *2.020,*2.021/*36, *2.001, *2.005, *2.012, *2.013, *2.018, *2.020, *2.021/*57]		E and G CYP2D7-2D6 +2D6/ CYP2D6-2D7	A/A/G	C/C/C	A/G	C/C/C	*13+*10/*36	0.25
*no call	*1/*4	1	2	2	1	1	2	1	2	(UND) [*1/*4x2, *1/*4.013+*4, *1/*4.013x2,...]		E CYP2D6-2D7 +2D6	G/G/G	T/C	A/A/G	C/C/C	*4.013+*4/*1	1

*The particular *13 sequence (GQ162807) to which these samples aligns has a switch region in intron 1.

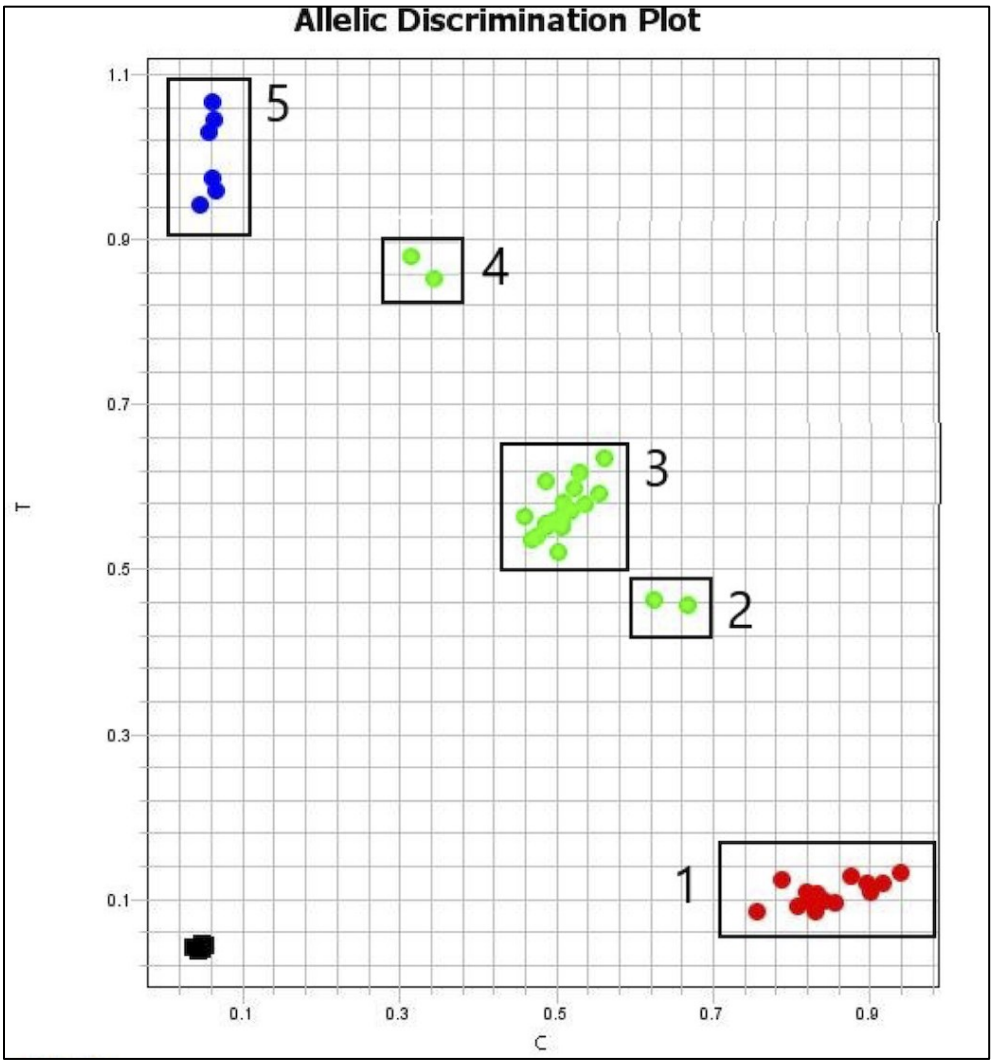
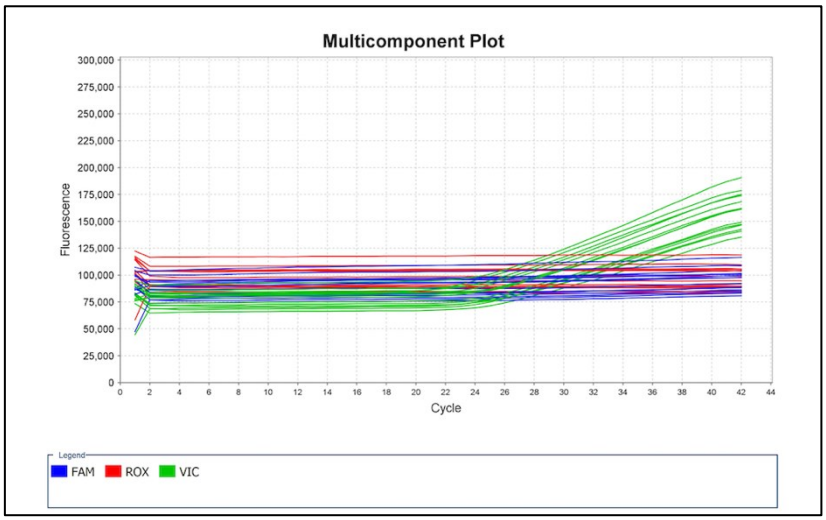
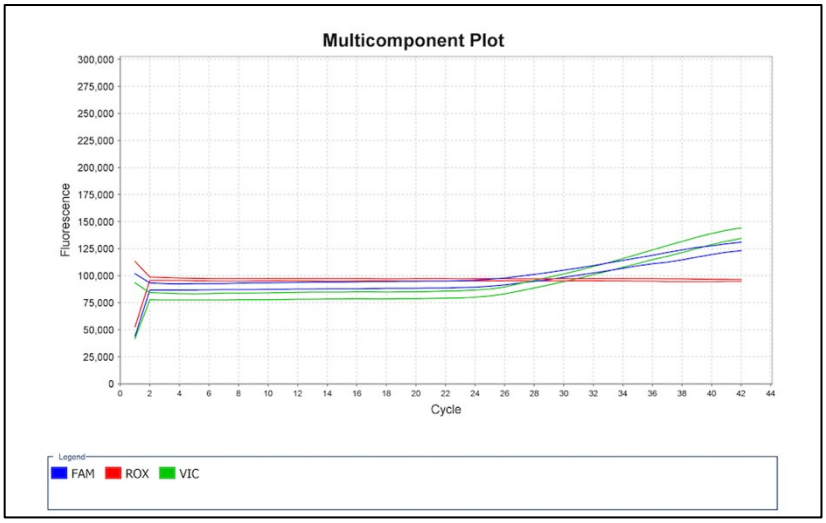


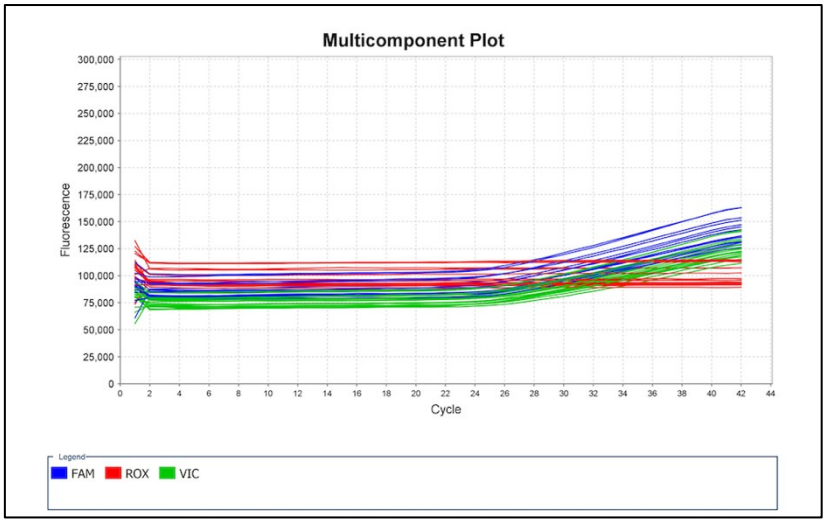
Figure S1A-F. TaqMan *CYP2D6*41* allelic discrimination plot (A), with multicomponent plots (B-F) showing different allelic ratios corresponding to the clusters marked 1-5. This is a C(Ref)>T(Var) SNV. In figures (B-F), the amplification for the reporter dye VIC labels the amplification of C (Ref), the amplification of FAM signals the presence of the T (Var), and ROX is present as a signal normalizsation tool.



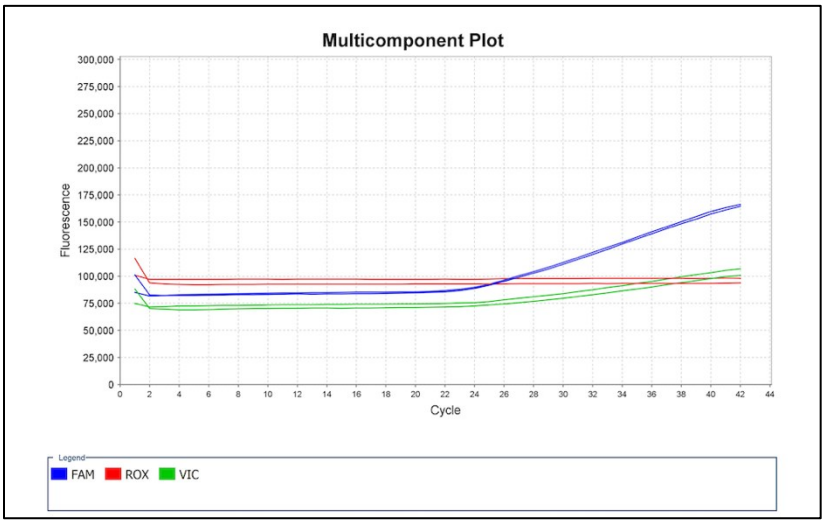
(B) Amplification of only C. Sample genotypes are **1/*1, *1/*1, *1XN/*1, *1X2/*2, *2X2/*1, *1X2/*5, *1X2/*35.*



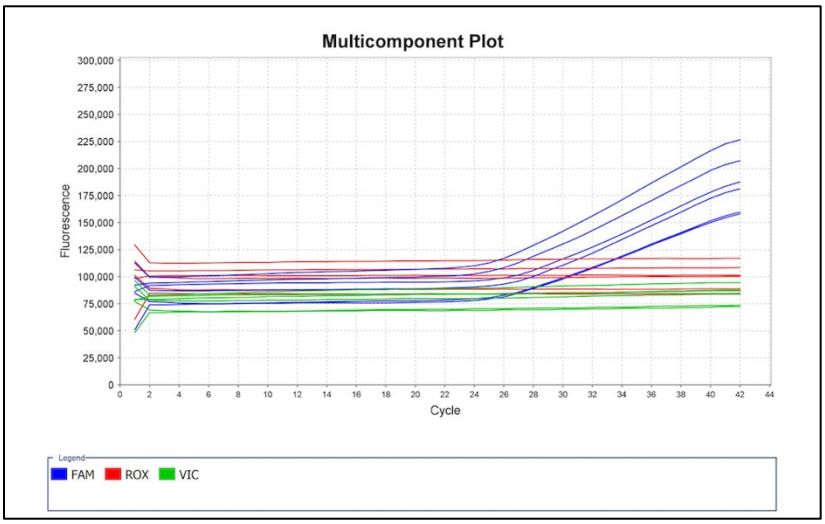
(C) Amplification of C and T, the former more than the latter, indicating a heterozygous **41* sample with more copies of C than T. Sample genotype is **2X2/*41*.



(D) Amplification of C and T to the same extent. Sample genotypes are **1/*41, *2/*41, *2/*41, *4/*41, *4/*41, *6/*41, *9/*41, *10/*41, *35/*41.*



(E) Amplification of C and T, the latter more than the former. Sample genotype is **41X3/*3*.



(F) Amplification of only T. Sample genotypes are **5/*41, *5/*41 *41/*41* (where **5* is a deletion of *CYP2D6*).

CHAPTER 4: Identification of a Previously Unreported *CYP2D6*41* Sub-Haplotype

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4.1 Abstract

Introduction: The phase I metabolic enzyme CYP2D6 is an important pathway for an estimated 20% of all currently prescribed drugs in medicine, thus of great interest to personalized medicine and, specifically, to pharmacogenomic efforts. Genotyping of the *CYP2D6* gene, which encodes the enzyme, has been historically challenging due to the highly polymorphic nature of this gene, including complex structural variants.

Methods: Following our reported cross-platform validation conducted with TaqMan CNV and SNV assays, Luminex xTAGv3 CYP2D6, PharmacoScan, the Ion AmpliSeq Pharmacogenomics Panel and Agena MassARRAY Veridose Core with *CYP2D6* CNV panel and some custom CNV assays, a sample of interest was put through L-PCR followed by Sanger sequencing of the resulting amplicon.

Results: While CNV data generated across the different platforms employed was concordant, the automated call of the sample of interest was not consistent across the available technologies. Sanger sequencing pointed to the presence of the main SNVs that characterize the *CYP2D6*41* haplotype: 2851C>T, 2989G>A, and 4181G>C. However, unlike in the other *CYP2D6*41* sub-haplotypes currently described, the SNV 1662G>C was not present.

Conclusion: Based on the sequencing data, with data on the SNVs corroborated by the previously used technologies, we report a newly characterized sub-haplotype of *CYP2D6*41*.

4.2 Introduction

Cytochrome P450 2D6 (CYP2D6) is a phase I metabolic enzyme responsible for the bioactivation or elimination of numerous drugs currently prescribed in medicine (Owen et al., 2009). It is estimated that about 20% (Caudle et al., 2020; Zanger et al., 2013) of all currently prescribed drugs involve CYP2D6 in their metabolism. Major classes of drugs included in this are: opioids (including prodrugs), antidepressants, antipsychotics, beta-blockers and anti-cancer agents (Henriques et al., 2020).

Of interest to psychiatry is the fact that CYP2D6 metabolizes a number of members of the two major antidepressant categories: tricyclic antidepressants (TCAs) such as nortriptyline, and serotonin selective reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluvoxamine, and fluoxetine. The same is true of first- and second-generation antipsychotics widely used in clinical practice, such as haloperidol, olanzapine and risperidone.

Currently, more than 140 haplotypes of the *CYP2D6* gene are known, and can be found at the Pharmacogene Variation Consortium (PharmVar) page (https://www.pharmvar.org/gene/CYP2D6). The extensive variability in *CYP2D6*, as exemplified by the number of haplotypes of this enzyme presents a challenge for genotyping that aims to determine a phenotype for an individual patient based on an identified diplotype. Given a diplotype, an individual can be classified as having enzyme activity equivalent to one of four metabolizer groups: poor (PM), intermediate (IM), normal (NM) or ultrarapid metabolizer (UM). This approach, however, has historically not been standardized, which has posed a challenge to the interpretation of the translation between genotype and metabolizer phenotype. More recently, a methodology to enhance genotype-phenotype translation of *CYP2D6* that takes into consideration the approaches of CPIC (the Clinical Pharmacogenetics Implementation Consortium), as well as that of the Dutch Pharmacogenetics Working Group (DPWG) has been

described (Caudle et al., 2020). This newly standardized approach uses the ascribing of an activity value to individual (*) haplotypes and translates the final sum of the values (the activity score) to one of the four phenotypic groups. Of note, CPIC and DPWG already use this approach, but Caudle et al. (2020) harmonized the scores associated with each level of metabolism, which was discrepant between the two consortia. The consensus was that an activity score (AS) of 0 corresponds to a PM level, AS between 0 and 1.25 to IM, AS between 1.25 and 2.25 to NM and an AS greater than 2.25 to the UM status. Having a consolidated translation system between the observed genotype by pharmacogenetic (PGx) testing platforms and metabolizer status is an important step in the implementation of prescribing strategies.

A consolidated strategy that converts laboratory results of haplotypes into metabolizer status needs to rely, however, on robust PGx results. Currently, there is a range of assays available for research use of *CYP2D6* that target the most common SNVs as well as other genetic events such as gene deletions and duplications. Examples of such assays are: the Ion AmpliSeq Pharmacogenomics Panel, PharmacoScan, the Luminex xTAGv3 CYP2D6 assay and the Agena MassARRAYVeriDose Core with CYP2D6 CNV or iPLEX CYP2D6. All of these were used on 95 samples from the Genome-based therapeutic drugs for depression (GENDEP) study, as part of a cross-validation exercise in order to generate methodology suitable for clinical genotyping of *CYP2D6* (Carvalho Henriques et al., 2021).

The Ion is a short-read next generation sequencing (NGS) technology that provides users with multiple known markers for single nucleotide variant (SNV) as well as copy number variant (CNV) analysis. Similarly, PharmacoScan also delivers information on CNVs, with its technology comprising microarray analysis of these and other markers (SNVs/indels). The Luminex technology likewise offers CNV and SNV/indel information and is based on a

workflow dependent on multiplex PCR amplification followed by multiplex allele specific primer extension (ASPE) and bead capture, which is capable of detecting clinically relevant haplotypes, and hence had IVD and Health Canada marking before its recent withdrawal from the market. Finally, the Agena MassARRAY, which may also provide CNV information, is based on mass spectrometric analysis of oligonucleotides. We used the VeriDose Core plus CYP2D6 CNV Panel Set, with custom assays for *CYP2D6*35, *40, *42*, **44*.

During this cross-validation, one of the samples, which was reported as having a consensus genotype of *CYP2D6*1/*41* (Chapter 3) (Carvalho Henriques et al., 2021), appeared to have a *CYP2D6*41* sub-haplotype that was not yet documented on PharmVar (PharmVar, 2021c). I, therefore, proceeded to analyze the sample by long-range polymerase chain reaction (L-PCR) followed by Sanger sequencing. Specifically, although the sample has the 2989G>A characteristic of *CYP2D6*41* haplotypes, it does not have the 1662G>C mutation that is found in all other *CYP2D6*41* sub-haplotypes identified to date. Table 4.1 outlines the data from each of the technologies described above.

Table 4.1 Comparative SNV calls across PharmacoScan, Luminex, Sanger sequencing, Ion AmpliSeq, TaqMan SNV and Agena data.

	Haplotype defining SNVs			Additional variants						
	2851C>T	2989G>A	4181G>C	1662G>C	-1770G>A	-1584C>G	-740C>T	221C>A	310G>T	3385A>C
PharmacoScan	HET	HET	HET	WT	HET	WT	HET	HET	HET	HET
Luminex	HET	HET	HET	WT	N/A	WT	N/A	N/A	N/A	N/A
Sanger sequencing	HET	HET	HET	WT	N/A	WT	HET	HET	HET	HET
Ion AmpliSeq	HET	HET	HET	WT	N/A	WT	N/A	N/A	N/A	N/A
TaqMan SNV	HET	HET	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Agena	HET	HET	HET	N/A	N/A	N/A	N/A	N/A	N/A	N/A

First described in 2000 (Raimundo et al., 2000), and further characterized in later years (Raimundo et al., 2004; Rau et al., 2006; Scantamburlo et al., 2017; Toscano et al., 2006), the *CYP2D6*41* haplotype results in reduced function of the encoded enzyme. This haplotype is characterized by the presence of the SNVs 2851C>T (R296C), 2989G>A and 4181G>C

(S486T); 2989G>A is a splice site defect in the intronic sequence of *CYP2D6*, thought to confer the reduced function characteristic of this haplotype (Raimundo et al., 2004). Further sub-haplotypes of this variant have been described in later years (**41.001, *41.002, *41.003, *41.004* and **41.005*), and currently five of those are catalogued by PharmVar (PharmVar, 2021c).

4.3 Materials and Methods

4.3.1 Samples

Ninety-five samples from the GENDEP (Genome-based therapeutic drugs for depression) study (Huezo-Diaz et al., 2012; Uher et al., 2009a) extracted from venous blood from individuals of self-reported European ancestry were previously analyzed using a) the AmpliChip CYP450 (Roche Molecular Systems, Pleasanton, CA, US), which was capable of identifying the following haplotypes: **2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40, *41, *114* (reported as **14A*) **1XN, *2XN, *4XN, *10XN, *17XN, *35XN, *41XN* and, b) TaqMan copy number variant (CNV) probes (assay IDs: Hs04083572_cn, Hs04502391_cn and Hs00010001_cn for intron 2, intron 6 and exon 9 respectively; Thermo Fisher Scientific). These samples were subsequently analyzed using the Luminex, Ion AmpliSeq, Agena MassARRAY, PharmacoScan and TaqMan SNV genotyping assays as part of the cross-validation work described above (Carvalho Henriques et al., 2021). The AmpliChip had returned no call for a sample of interest, which also occurred for the Luminex and Ion AmpliSeq, while PharmacoScan and Agena gave **1/*41*.

4.3.2 CNV analysis

TaqMan CNV probes designed to target intron 2 (Hs_04083572; Chr22:42129681), intron 6 (Hs_04502391; Chr22:42127680) and exon 9 (Hs_00010001; Chr22:42126649) of the *CYP2D6* gene were used to conduct CNV analysis of the GENDEP sample set and were run on a ViiA7

machine (Thermo Fisher Scientific). A reaction volume of 10 µl was used, with reaction conditions as follows: 95° for 10 minutes, followed by 40 cycles of 95° for 15 seconds and 60° for 1 minute. Samples were run in replicates of at least two as per the manufacturer's recommendation. Data were analyzed by Copy Caller Software, version 2.1. (Thermo Fisher Scientific), using a calibrator sample of copy number 2 and known genotype relevant to each of the above CNV probes. The CNV call confidence level was at least 95%, most being above 99%.

4.3.3 Ion AmpliSeq

Genotyping using the Ion AmpliSeq Pharmacogenomics Panel (Thermo Fisher Scientific) was conducted according to the manufacturer's instructions using an Ion Chef instrument (Thermo Fisher Scientific, Waltham, MA, USA). Short stretches of genomic DNA were sequenced, including regions of *CYP2D6* designed to detect gene deletion, duplication and conversion (*CYP2D6-2D7* hybrid) events, followed by digestion of the resulting amplicons, which were ligated to barcode adaptors (Ion Express barcode adaptors 1-96 kit, Thermo Fisher Scientific) and purified using the AMPure XP Reagent (Beckman Coulter, Mississauga, ON, Canada).

Library quantification was performed using the Ion Library TaqMan Quantitation Kit (Thermo Fisher Scientific). GeneStudio Data Analysis software (Thermo Fisher Scientific) was used for data analysis. On average, the Ion AmpliSeq run resulted in 109,454 reads per sample. The run generated information on genotyping of *CYP2D6* related to the presence of various SNVs, as well as CNV data based on exon 9 of *CYP2D6*, and a *CYP2D6* gene-level CNV call based on the average of data from nine amplicons at the following genomic locations Chr22:42523660- 42523817, 42523846-42524010, 42524298-42524433, 42524513-42524640, 42524932- 42525095, 42525131-42525245, 42525274-42525382, 42525575-42525688 and 42526621-42526808.

CYP2D6 Haplotype Translators© ("CYP2D6 & CYP2C19 Haplotype Translator Tools," 2021; Yavorskyy et al., 2021) may be used to derive *CYP2D6* genotypes using the AlleleTyper software (Thermo Fisher Scientific).

4.3.4 PharmacoScan

The PharmacoScan, assay was run by Neogen (Neogen Canada, Edmonton working with Neogen Genomics, Nebraska, USA). Data analysis of the resulting variants was conducted using Axiom Analysis 4.0.3.3 (using the r9 version of the *CYP2D6* translator; Thermo Fisher Scientific). CNV calls were provided by probes for exon 9 of *CYP2D6* as well as for the 5' and 3' flanking regions as described (Carvalho Henriques et al., 2021; Gaedigk et al., 2019).

4.3.5 Luminex

The Luminex xTAG CYP2D6 v3 research use only kits were applied to the samples and run according to the manufacturer's instructions on a Luminex 200 system (Luminex Molecular Diagnostics, Inc., Toronto, ON, Canada). Haplotypes covered for CYP2D6 are: *CYP2D6*2-*12* (including the **5* gene deletion), **14, *15, *17, *29, *35, *41*, and gene duplications. Additional haplotypes (**14, *39, *69*, and **114*), sub-haplotypes (**1.011, *2.001/*2.005/*2.012/*2.013/*2.018/*2.020/*2.021, *2.004, *4.002, *4.012, *6.003, *12.001, *12.002, *39.001, *39.002*), hybrid haplotypes (**4.013,* two specific **13s, *36, *57, *68* and **83*) and hybrid tandems (**4.013+*4, *4.013x2+*4, *4.013+*4x2, *4.013x2+*4x2, *36+*10, *36+*10x2, *36x2+*10, *36x2+*10x2*) can be derived using a *CYP2D6* Haplotype Translator© ("CYP2D6 & CYP2C19 Haplotype Translator Tools," 2021).

4.3.6 Agena MassARRAY

The Agena MassARRAY (Agena Bioscience, San Diego, CA) Veridose Core plus *CYP2D6* copy number variant (CNV) panel including 18 *CYP2D6* variants plus gene deletion, duplication and

CYP2D6-2D7 conversion events was used. In addition, we ran five custom assays for *CYP2D6*: **25, *35, *40, *42*, and **44*. Genomic DNA was subjected to PCR followed by single-base extension with the extension products then being dispensed onto a SpectroCHIP Array and detected via mass spectrometry as described (Gaedigk et al., 2019). Haplotypes were assigned using Typer Analyzer software version v4.1.83 (Agena Bioscience).

4.3.7 TaqMan SNV Probes

TaqMan assays for relevant SNVs were run for haplotypes *CYP2D6*2, *3, *4. *6, *35* and **41* (assay IDs C_27102425_10, C_32407232_50, C_27102431_D0, C_32407243_20, C_27102444_F0, and C_34816116_20, respectively). These correspond to 2851C>T (rs16947), 2550delA (rs35742686), 1847G>A (rs3892097), 1708delT (rs5030655), 31G>A (rs769258) and 2989G>A (rs28371725).

4.3.8 Long Polymerase Chain Reaction (PCR)

The sample of interest was submitted to Sanger sequencing commencing with an allele-specific long-PCR method of amplifying the *CYP2D6* gene and its 5' flanking region as described (Gaedigk et al., 2015). This uses a forward primer specific for the genotype at the -1584C>G variant. Data from the genotyping technologies above described indicated the call at this base was -1584C. Primers therefore were 5′-CCTGGACAACTTGGAAGAACCC-3′ (-1584C>G) and 5′-CGACTGAGCCCTGGGAGGTAGGTAG-3′ (known as the "universal fragment A reverse primer"). A subsequent run was performed using the same forward primer described above, but with a reverse primer of my own design (2D6-R): 5'-GAGCCCTGGGAGGTAGGTAG-3'. This later run was used to compare sequencing information as well as allele specificity.

Using the KAPA HiFi HotStart Ready Mix kit (which contains 2.5 mM $MgCl_2$ and 0.3 µM dNTPs at final concentration) with 25µl of Master Mix, 1.5µl of each primer at 10µM , 1.5µl

of dNTPs at 10µM (ThermoFisher), 0.5µl of $MgCl_2$ at 25mM (ThermoFisher), 16µl of water, 1µl of DMSO and 3µl of template, reaction conditions were: initial denaturing at 95°C for 3 min; followed by 10 cycles of 98°C for 10 sec and 69°C for 6.5 min; then 25 cycles of 98°C for 15 sec and 69°C for 6.5 min; with a terminal extension step of 72°C for 7 min. At final concentration, each primer was at 0.3 µM, dNTPs at 0.6 µM, $MgCl_2$ at 2.75 mM, and DMSO at 2%.

4.3.9 Sanger Sequencing

The long-PCR product for the -1584C>G long-PCR was run on a 0.75% agarose gel, with amplicon purification by gel extraction (GeneJET Gel Extraction Kit, Thermo Fisher Scientific, Waltham, MA). Purified DNA was submitted for Sanger sequencing (Table 4.2). Resulting sequencing products were aligned with the *CYP2D6*41* haplotype sequence deposited on the National Center for Biotechnology Information (NCBI), accession number DQ282160. The alignment (Figure 4.1 A, B, C) was conducted using SnapGene Viewer 5.1.3.1 software.

4.4 Results

Copy number analysis from TaqMan resulted in a call of 2 across the three probes used for intron 2, intron 6 and exon 9. Additionally, PharmacoScan also showed an equal call across its three CNV probes. Concordant with the above, Ion AmpliSeq CNV analysis returned a call of 2 at both exon 9 and the gene level.

The PharmacoScan *CYP2D6* translator (r9) gave a genotype of *CYP2D6*1/*41*, supported by both the Agena and Luminex data, the genotype from the latter being generated through manual calling ignoring the 1662G>C as this is not a defining variant for the *CYP2D6*41* haplotype. The Luminex data showed a heterozygous call for the SNVs (nucleotide positions given in PharmVar nomenclature) 2851C>T, 2989G>A, and 4181G>C, with wild-type at 1662G>C (Table 4.1). The automated calling algorithm failed as it includes 1662C for

*CYP2D6*41*. The TaqMan SNV data likewise gave a heterozygous call for the assays for rs16947 (2851C>T) and rs28371725 (2989G>A) (Table 4.1). Unlike PharmacoScan, no translation was available from Ion AmpliSeq using the current version of the translators, as these include 1662C for *CYP2D6*41*. After manually adjusting the current translator by replacing the previous entry for **41* by an entry for **41new* where no mutation occurred at the 1662 locus (1662G, entered in the translator as 1662C, complementary strand), the adjusted translator generated a call of **1/*41new*.

Table 4.2 List of primers used for L-PCR and Sanger sequencing of the novel *CYP2D6*41* sub-haplotype

Primer Name	Primer Sequence	Reference
-1584C-F	CCTGGACAACTTGGAAGAACCC	Gaedigk et al., 2015
-1584G-F	CCTGGACAACTTGGAAGAACCG	Gaedigk et al., 2016
Universal fragment A reverse primer	CGACTGAGCCCTGGGAGGTAGGTAG	Gaedigk et al., 2015
-740C-F	TGTGTGTGAGAGAGAATGTGTGCC	Gaedigk et al., 2015
1163F	CTCATGCCTATAATCCCAGC	Gaedigk correspondence
2908R	TGGCTCCCCTCCATTGTGC	Gaedigk correspondence
3131F	GGATCCTCCATAACGTTCCCACC	Gaedigk correspondence
3526F	TGTAATCGTGTCCCTGCAAG	Gaedigk correspondence
3625R	GACATGCACAGACGCTATGC	Gaedigk correspondence
2D6-L-DF	CCAGAAGGCTTTGCAGGCTTCAG	Gaedigk et al., 2010
P1	TCCCCCACTGACCCAACTCT	Sachse et al., 1997
FE2	GGCCCTGACCCTCCCTCTGC	Broly et al., 1995
RE2	CTCTGTCCCCACCGCTGCTT	Broly et al., 1995
RE3	GCCCTTCTGCCCATCACCC	Broly et al., 1995
FE4	CCCGCATCTCCCACCCCC	Broly et al., 1995
RE4	CCTCGGTCTCTCGCTCCGC	Broly et al., 1995
FE5	GACCCCGTTCTGTCTGGTGT	Broly et al., 1995
RE5	CCGTGGCAGCCACTCTC	Broly et al., 1995
FE6	GTATGCTCTCGGCCCTGCTC	Broly et al., 1995
RE6	ACTGTTTCCCAGATGGGCTC	Broly et al., 1995
FE7	GTGGGGACGCATGTCTGTCC	Broly et al., 1995
RE7	GGAGGGCGCCAGGCCT	Broly et al., 1995
FE8	TCACCCTGCATCTCCTGCCC	Broly et al., 1995
RE8	CCGGGCTCCCCACAGGC	Broly et al., 1995
RE9	TGGGGACTAGGTACCCCATT	Broly et al., 1995
9F	CTTTGTGCTGTGCCCCGCTAG	Aitchison, 2003
9F-RC	CTAGCGGGGCACAGCACAAAG	Aitchison, 2003
1R	GTCCACCAGGAGCAGGAAGAT	Aitchison, 2003
1R-RC	ATCTTCCTGCTCCTGGTGGAC	Aitchison, 2003
4573R	CCCTTGCCCTACTCTTCCTT	**
1429F	GTCTTCCCTGAGTGCAAAGG	*
3988R	CTCAACGTACCCCTGTCTCA	*
2398F	TCAGTGGTAAGGACAGGCAG	*
1697F	GCTGGAGCAGTGGGTGAC	*
477R	CCCACTCCAGAGTGACCTTC	*
510R	CGTGATTTAAACGGCACTCA	*
451F	AAGTCCCTTCTGCTGACACC	*
1185R	TCCCTAGTGCAGGTGGTTTC	*
3426R	GTGGCCAGGGTTCCTAGAGT	*
2D6-R	GAGCCCTGGGAGGTAGGTAG	*
-740T	TGTGTGAGAGAGAATGTGTGCT	*

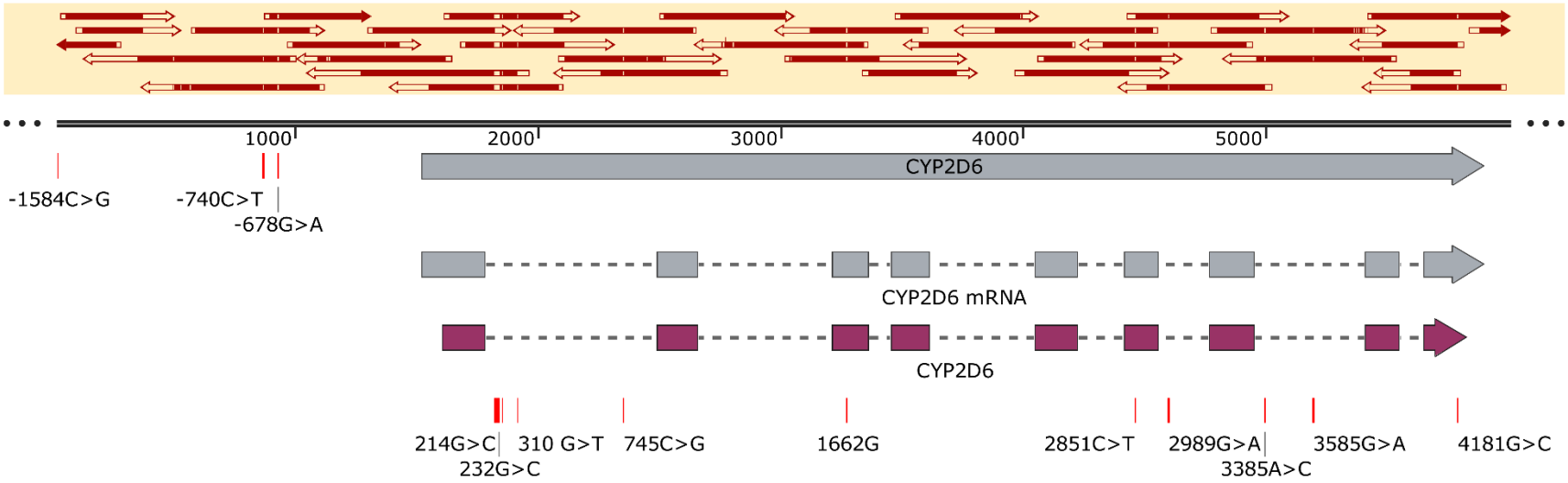

Figure 4.1 A Sequence alignment for the sample of interest to the *CYP2D6*41* reference sequence (GenBank accession number DQ282160). Heterozygous bases in the data are marked up, together with the base showing 1662G/G.

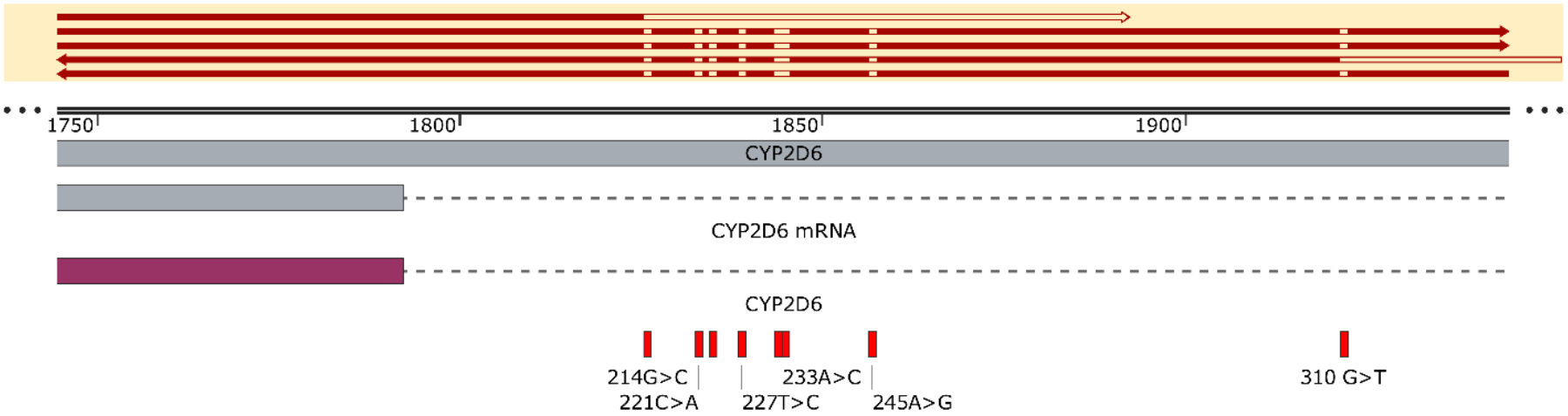

Figure 4.1 B Augmented sequence alignment of sample of interest to the *CYP2D6*41* reference sequence highlighting the 214-245 SNV cluster. In addition to the SNVs depicted in the figure, the following are marked but not labeled: 223C>G and 232G>C.

Figure 4.1 C Chromatogram of the sequence alignment for the 214-245 SNV cluster.

The heterozygous calls for the sample for the above SNVs according to the various technologies (Table 4.1) were consistent with the Sanger sequencing results.

Highlighted in Figures 4.1A and B are the SNVs detected by Sanger sequencing. Heterozygosity was detected at the site of each SNV (Figure 4.1A, B and C), suggesting the presence of the two alleles in the amplification. This was despite the products of the allele-specific L-PCR appearing to be relatively allele-specific with an annealing and elongation temperature of 69^0C on agarose gel electrophoresis (Figure 4.2).

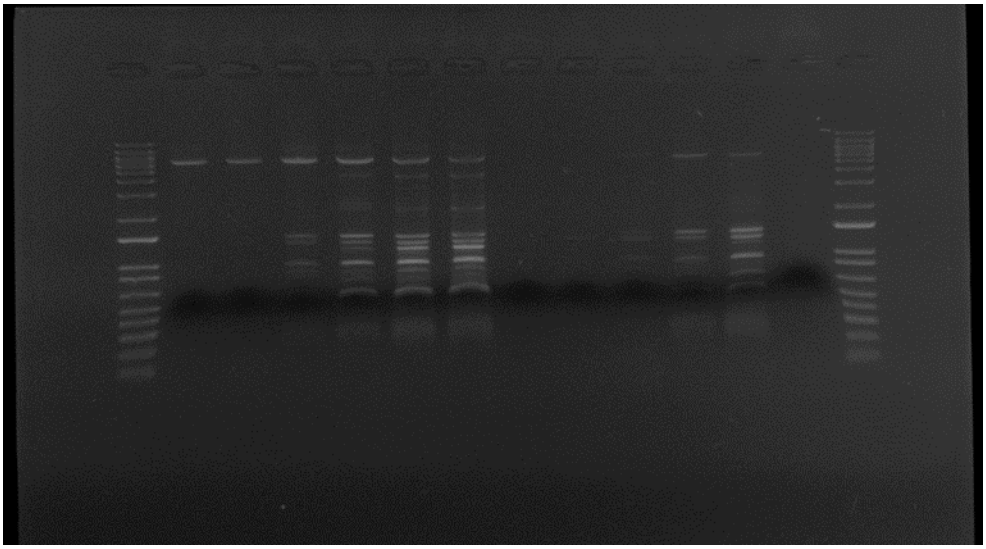

Figure 4.2 Gel image for amplification using the -1584C and -1584G versions of the forward primers (Table 4.1). Lanes 1-6 represent the results using the-1584C, varying annealing temperature from 70° (left) to 65° (right). Lanes 7-12 show the results using the -1584G, varying the annealing temperature from 70° (left) to 65° (right).

From the data generated by Sanger sequencing at SNVs with a homozygous call, I was able to compare the occurrence or absence of defining SNVs of the currently known sub-haplotypes of *CYP2D6*41,* uncovering a pattern for the sample that did not correspond to the existing sub-haplotypes (Table 4.3). Further, the sequencing data was compared to the currently known haplotypes that include the splice site mutation 2989G>A (Table 4.4). Each haplotype has a group of SNVs that characterize them; the three heterozygous SNVs identified in the

sequencing and corroborative cross-platform data were consistent with a *CYP2D6*41* and not with any of the other haplotypes with the 2989G>A substitution.

Table 4.3 Comparison between defining SNVs of existing *CYP2D6*41* sub-haplotypes and their occurrence on the inferred novel *CYP2D6*41* sub-haplotype

	-431C>T	1378C>G	1614C>T	1662G>C	2471T>C	4016C>A
Novel sample data	C/C	C/C	C/C	G/G	T/T	C/C
Novel sub-haplotype	C	C	C	G	T	C
CYP2D6*41.001				C		
CYP2D6*41.002				C	C	
CYP2D6*41.003				C		A
CYP2D6*41.004		G	T	C		
CYP2D6*41.005	T	G	T	C		
		= SNV absent in the sub-haplotype				

Table 4.4 Comparison between data from the novel sample including haplotype inference versus SNV patterns of haplotypes with the 2989G>A substitution

	100C>T	1736G>C	2851C>T	2870T>C	2989G>A	3854G>A	4145G>A	4181G>C
Novel sample data	C/C	G/G	C/T	T/T	G/A	G/G	G/G	G/C
Inferred novel haplotype	C	G	T	T	A	G	G	C
*32								
*41								
*69								
*91								
*119								
*123								
*138								

= SNV not present in the haplotype

= Haplotype defining SNV

4.5 Discussion

Following the analysis of 95 samples of interest from the GENDEP study, we have found and characterized a sample with a novel *CYP2D6*41* sub-haplotype not previously described on PharmVar.

The AmpliChip prior data gave no indication of genotype and hence metabolizer status for this patient. Therefore, from the prior data, there was no indication as to the genotype and, consequently, metabolizer status of this individual. Importantly, the discontinued AmpliChip used a methodology for identifying *CYP2D6*41* haplotypes which differed from current technologies, as it was based on the identification of the following SNVs (nucleotide positions given in PharmVar nomenclature): 1662G>C, 2851C>T, and 4181G>C. It did not include identification of the key functional SNV in *CYP2D6*41*, the 2989G>A (splice defect) as this was published after the development of the AmpliChip assay (Raimundo et al., 2004). As our sequencing and genotyping information has shown, the current sample did not, in fact, carry the 1662G>C mutation, hence the AmpliChip no call. This weakness of the AmpliChip assay has been noted by other investigators (Bank et al., 2018b).

Using methodology described previously, an approach based on TaqMan CNV probes was performed to identify potential *CYP2D6* structural variants. Alongside TaqMan, the technologies PharmacoScan and Ion AmpliSeq interrogated *CYP2D6* copy number in the same (exon 9) region of the gene and in complementary regions. We thus demonstrated no anomalous calls or calls higher than 2 across any of the platforms, indicating the absence of a *CYP2D6* structural variant.

In addition, the genotype of the sample in question was explored using the Ion AmpliSeq, PharmacoScan, Agena MassARRAY and Luminex assays. For PharmacoScan and Agena, the output was a call of **1/*41*. This call suggests the combination of a normal metabolizer and intermediate metabolizer haplotype, generating an AS call of 1.5, according to Caudle et al. (2020). The automated calls for Ion AmpliSeq and Luminex were no translation available and no call, respectively. PharmacoScan, Luminex, and Ion AmpliSeq provided additional genotyping

information that showed the presence of a *CYP2D6*41*, where the sample was heterozygous for the haplotype defining SNVs 2851C>T, 2989G>A and 4181G>C, but unlike any prior *CYP2D6*41* sub-haplotype, was wild-type for the 1662G>C variant (Table 4.1).

Sequencing confirmed the presence of the *CYP2D6*41* haplotype defining SNVs (2851C>T, 2989G>A, 4181G>C), as listed in the PharmVar website and the fact that the SNV 1662G>C, currently listed in all *CYP2D6*41* haplotypes from *CYP2D6*41.001* to *CYP2D6*41.005*, was not present. Further consensus between the platforms indicated the presence in heterozygosity of the SNVs -740C>T and 3385C>T.

Sequencing data demonstrated the presence of heterozygosity for the following SNVs, which, based on comparison data of the existing **1* and **41* haplotypes, were assigned to the novel *CYP2D6*41* haplotype: -1584C>G, -740C>T, -678G>A, 214G>C, 221C>A, 223C>G, 227T>C, 232G>C, 233A>C, 245A>G, 745C>G, 2851C>T, 2989G>A, 3385A>C, 3585G>A, and 4181G>C. PharmacoScan data additionally identified an SNV at position -1700; however, as this variant is not catalogued by PharmVar, I was not able to assign this to one or another haplotype.

Table 4.3 demonstrates discrepancies between the currently described sub-haplotypes of **41* with the novel one described in this paper. Importantly, Sanger sequencing data for SNVs for which the data were homozygous wild-type were compared with data for these SNVs in other haplotypes with the 2989G>A SNV, namely, **32, *69, *91, *119, *123* and **138*. In accordance with the genotyping calls above, these other haplotypes were ruled out due to the absence of at least one SNV that defining them (Table 4.4).

Of note is the fact that, in a recent study (Manoharan et al., 2019), the haplotype *CYP2D6*41* was found as the most frequent haplotype following normal function **1* and **2* in an Indian population. Additionally, the high frequency of this haplotype in Middle Eastern and

Sub-Saharan African peoples has been highlighted (LLerena et al., 2014; PharmGKB, 2021e). The results we describe here, then, not only add to the current body of work related to *CYP2D6* and its many haplotypes, but may also be of particular relevance for these populations.

4.6 Limitations

The work described herein has the following limitations. Firstly, there is the fact that the L-PCR amplification to which the sample of interest was submitted does not seem to be as allele-specific as was expected. While at the PCR stage, when comparing the results generated by different versions of the forward primer that are designed to match different alleles of the mutation at the -1584C>G substitution, it appeared on agarose gel electrophoresis that the amplification was relatively specific (Figure 4.2). However, on reviewing the generated sequencing data, at the SNVs of interest there was a heterozygous call, pointing to the non-specificity of the amplicon and the presence of the two alleles in the resulting data. While subsequent L-PCR runs were explored, using a novel 3' end primer as the reverse primer (2D6-R, as described in Table 4.2) and another forward primer, which explored the -740C>T SNV (740T as described in Table 4.2) aiming to generate a more truly allele-specific reaction, specificity was still not obtained in sequencing data for these different trials. Reaction mix conditions for these were the same to the one described under the L-PCR section of this chapter, with the forward primer being the -740T. Cycling conditions were as follows: initial 95°C for 3 min, followed by 10 cycles of 98°C for 10 sec and 68°C for 6 min, then 25 cycles of 98°C for 15 sec and 68°C for 6 min, and a final extension of 72°C for 7 min. Nonetheless, based on the existing data for sub-haplotypes of *CYP2D6*1* and *CYP2D6*41,* I was able to infer the assignment of the SNVs detected to the two haplotypes.

4.7 Conclusion

In summary, based on a multiplatform approach that included TaqMan CNV and SNV probes, PharmacoScan, Ion AmpliSeq, Luminex and Agena MassARRAY, as well as sequencing of the amplified *CYP2D6* gene, a novel *CYP2D6*41* sub-haplotype has been identified. Despite the limitations of the approach taken, owing to prior data, haplotype inference was possible. Confirmatory data could be generated by making the allele-specific L-PCR truly allele-specific and/or by using a single molecule long-read sequencing technology such as that provided by the PacBio system.

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CHAPTER 5: Conclusion

Summarized in the review paper *How Can Drug Metabolism and Transporter Genetics Inform Psychotropic Prescribing?* (Chapter 2) are important considerations relevant to drug-gene pairs and drug-drug interaction effects for clinical practice. In offering an overview of the main enzymes and transporters involved in phases I, II and III, we present evidence about which of these targets are relevant to which psychotropic drugs. Building on this, we provide more detail about the gene-drug pairs including specific haplotypes relevant to pharmacogenetics in psychiatry.

While the evidence presented on genetic background information important for psychiatric clinical practice involves the CYP family as a whole, for *CYP2D6* and *CYP2C19* not only is there a clear phenotypic-genotypic relationship, but also there are associations with clinical outcomes such as measures of exposure to drug (e.g., concentration of drug and/or metabolites). Hence, the majority of actionable information for psychotropics is related to these two enzymes and to the genes that encode them, *CYP2D6* and *CYP2C19*. The two enzymes and their gene-drug pairs have robust guidelines by both CPIC and DPWG, especially where antidepressant prescribing is concerned.

The challenge that remains from the review is how to action the information gathered in it in clinical practice. While there are a number of commercial tests currently available, prior to the publication of Chapter 2, there was no consensus regarding variant coverage, methodology or interpretation of results.

With the question of varied methodology in mind, *Methodology for clinical genotyping of CYP2D6 and CYP2C19* (Chapter 3) further looks at the importance of these two enzymes by establishing validated methodology for genotyping both genes suitable for clinical implementation. Historically, *CYP2D6* more so than *CYP2C19* has been challenging to genotype

due to extensive polymorphism - more than 140 haplotypes, including sequence that represents *CYP2D7* conversion events and other structural variation, making it difficult for different technologies to comprehensively identify all the haplotypes that are above a frequency of 1% in the population. The relevance of *CYP2C19* to psychiatry warranted the inclusion of this gene in the methodological investigation described in the chapter.

While the whole of the GENDEP samples had been previously genotyped with the AmpliChip, the 95 samples selected for the study were enriched for structural variants and genotypes that had been challenging to identify. This was done through screening of samples with TaqMan CNV probes and selection of those with calls that differed from a wild-type call. The use of multiple genotyping platforms - TaqMan CNV and SNV assays, Luminex xTAGv3 CYP2D6 and CYP2C19, PharmacoScan and the Ion AmpliSeq Pharmacogenomics Panel, as well as Agena MassARRAY (with data available mainly for *CYP2C19*) - for the identification of these 95 samples served the purpose of cross validating these same platforms. In addition, we provide a novel method of identifying *CYP2D6*13* hybrid haplotypes from multiplex genotyping of amplicons with the resultant patterns of SNV data that could be adapted for use with other genotyping technologies, and is included in our *CYP2D6* Haplotype Translators ©.

Structural variants identified by the CNV screening described above included hybrids representing a part from *CYP2D6* and a part from *CYP2D7*. Chapter 3 includes the L-PCR amplification and the subsequent Sanger sequencing that was applied to such hybrids. As hybrids have been of interest to pharmacogenetic research, but remained challenging to identify, this is an important contribution to the pharmacogenetics of *CYP2D6*. Indeed, to date not all hybrids are catalogued on PharmVar, and not all have an assigned function.

In Chapter 4, the work conducted previously for the characterization of the 95 selected samples was taken further for one sample of interest. In this instance, the platforms used for genotyping of the sample were not concordant in their call. While the PharmacoScan translator resulted in a call of *CYP2D6*1/*41* genotype, Luminex and the Ion AmpliSeq did not generate an automatic call for the sample in question, although manual calling with Luminex later provided a call concordant with PharmacoScan, whilst acknowledging that the automated call had not been generated owing to the absence of the 1662G>C. The sample therefore appeared to have a novel *CYP2D6*41* sub-haplotype. To answer the question of the genotype of this sample, the approach used was similar to that used for the hybrids in Chapter 3, i.e., L-PCR amplification followed by Sanger sequencing.

5.1 Limitations

The work described in Chapters 3 and 4 conducted in the Aitchison lab relied on the use of the GENDEP samples, a study in which participants were of European ancestry. This characteristic of the sample set is a limitation of the studies described herein, as both the frequency of the haplotypes and the actual haplotypes encountered are limited to populations of the same ancestry, even though haplotypes such as *CYP2D6*36* not commonly associated with European populations were reported, pointing to likely admixture in the sample set. Therefore, the work that was conducted can be used as a reference to future lines of investigation in populations of different ethnicity.

5.2 Future directions

The further genotyping and characterization of the sample of interest described in Chapter 4 could benefit from the use of single molecule real-time sequencing (SMRT) technology. This

technology now has long-read (an average of 13.5 kb) and high fidelity (>99%) capability (Wenger et al., 2019). Building on the methodology described here, it is our goal to use the L-PCRs that we have developed in Chapter 4 to amplify the entire *CYP2D6* gene and its 5' and 3' flanking sequence using primers 5'- CCTGGACAACTTGGAAGAACCC -3' and 5'-GAGCCCTGGGAGGTAGGTAG -3' respectively, and sequence this using this technology. This will enable reliable haplotyping, validating the results we presented.

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