CHAPTER

1

Principles of Pharmacogenomics: Pharmacokinetic, Pharmacodynamic, and Clinical Implications

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OBJECTIVES

1. Describe how a single-nucleotide polymorphism (SNP) can affect protein function or expression, and consequently, influence drug response.
2. Explain how genetic polymorphisms for drug metabolism or drug-transporter proteins may influence drug pharmacokinetics.
3. Contrast phenotypic responses to genetic variation for drug metabolism versus drug-target proteins.
4. Describe novel drug developed based on an understanding of genes involved in disease pathophysiology.
5. Explain how genetic polymorphisms at the drug-target site may influence drug pharmacodynamics.

INTRODUCTION

Significant interpatient variability in drug response is largely attributed to innate differences among individuals in their capacity to process and respond to medications. Pharmacogenomics involves incorporating information about a person's genotype into drug therapy decisions, with the goal of providing the most effective and safest therapy for that individual. Over the last decade, there have been significant advances in our understanding of the contribution of genetic differences in pharmacokinetics and pharmacodynamics toward interindividual variability in drug response. Not only may pharmacogenomics lead to improved use of existing therapies, but it may also lead to novel drugs developed based on an improved understanding of genetic control of cellular functions.

The human genome comprises approximately 20,000 protein-coding genes. By far the most common variation is the single-nucleotide polymorphism (SNP), which is defined as single-base differences that exist between individuals. Over 22 million SNPs have been reported in the human genome [1]. SNPs that result in amino acid substitution are termed nonsynonymous. Nonsynonymous SNPs occurring in coding regions of the gene (e.g., exons) can impact protein activity and have significant consequences on responses to medications that depend on the protein for metabolism, transport, or eliciting cellular effects. Synonymous polymorphisms do not result in amino acid substitution; however, those occurring in a gene regulatory region (e.g., promoter region, intron) may alter gene expression and the amount of protein that is produced. Two or more SNPs are often inherited together more frequently than would be expected based on chance alone. This is referred to as linkage disequilibrium (LD). A haplotype refers to a set of SNPs that are in LD. Other types of variation that can affect gene expression or protein conformation include insertion–deletion polymorphisms (indels), short tandem repeats, and copy number variants (CNVs). A CNV represents a DNA segment (≥1 kb) with a variable number of copies of that segment, because of duplications, deletions, or rearrangement, and constitutes a major source of interindividual variation in the human genome. A unique reference SNP identifier (rs number) is assigned for each genetic variant, and exists as an SNP data repository, the National Center for Biotechnology Information (NCBI) Single-Nucleotide Polymorphism Database (dbSNP).

Polymorphisms commonly occur for genes encoding drug metabolism, drug transporter,

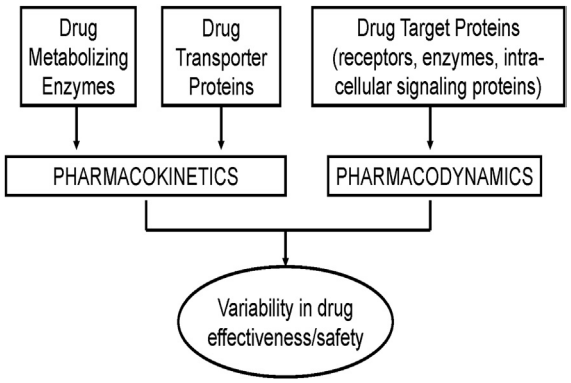

FIGURE 1.1 Location of genetic variations affecting drug response. Those occurring in genes for drug metabolism or transport can affect drug pharmacokinetics, whereas SNPs in genes encoding for drug-target proteins can impact drug pharmacodynamics.

and drug-target proteins (Fig. 1.1). Drug metabolism and transporter genotypes can affect drug availability at the target site, whereas drug-target genotype can affect a patient's sensitivity to a drug. In many instances, genes for proteins involved in drug disposition, together with genes for proteins at the drug-target site, jointly influence drug response. In addition, genetic polymorphisms in absorption, distribution, metabolism, and excretion (ADME) and target genes also contribute to ethnic heterogeneity in drug response [2]. Research advances have resulted in continued identification of association between genetic polymorphisms and response, with recent focus on genome-wide association studies (GWAS) in populations worldwide.

The terms pharmacogenetics and pharmacogenomics are often used interchangeably. Because drug responses are mostly determined by multiple, rather than single, proteins, recent trends of investigations on determinants of drug response have shifted from pharmacogenetics to pharmacogenomics. However, for simplicity, this chapter treats pharmacogenetics and pharmacogenomics as synonymous.

Despite the scientific advances made, personalized medicine envisioned many years ago has in many cases yet to become a reality. Exceptions to this largely exists in oncology and more recently in cardiology, in which genotyping to determine clopidogrel effectiveness is starting to become routine at some large academic medical centers [3,4]. Examples of genotype-guided therapies are beginning to emerge in other therapeutic areas, which are discussed in detail throughout this book. However, significant challenges still exist in ethical, socioeconomic, regulatory, legislative, drug development, and educational issues that need to be addressed and resolved before personalized medicine can be practically and satisfactorily implemented in clinical practice on a broader scale. The goal of this chapter is to review the pharmacokinetic and pharmacodynamics basis of individualized therapy, and briefly discuss the challenges of implementing pharmacogenomics in clinical practice. Further indepth discussion of specific therapeutic areas and/or disease states, as well as ethical, socioeconomic, regulatory, legislative, drug development, technological, and educational issues will be the focus of subsequent chapters.

POLYMORPHISMS IN CYTOCHROME P450 ENZYMES

The cytochrome P450 (CYP) superfamily of isoenzymes represents the most important and studied metabolic enzymes that exhibit clinically relevant genetic polymorphisms. Within this superfamily of isoenzymes, 57 different CYP genes and 58 pseudogenes have been identified, and, based on the similarity in their amino acid sequences, are grouped into 18 families and 44 subfamilies with increasing extent of sequence similarity. Of these genes and pseudogenes, 42 are involved in the metabolism of exogenous xenobiotics and endogenous substances, such as steroids and prostaglandins, and 15 are known to be

involved in the metabolism of drugs in humans [5]. Information regarding *CYP* allele nomenclature and specific genetic variations defining different metabolic phenotypes had been available at the Karolinska Institute website: www.cypalleles.ki.se, for more than a decade, and recently moved to the new Pharmacogene Variation (PharmVar) Consortium, which serves as a new hub for pharmacogene nomenclature [6].

The genes encoding CYPs are highly polymorphic, with SNPs in the *CYP* gene locus accounting for most of the variations in CYP activity, resulting in functional genetic polymorphism for several isoenzymes, including CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Additional types of *CYP* polymorphisms cause gene deletions, deleterious mutations resulting in premature stop codon or splicing defects, amino acid changes, gene duplications, and CNV. Different alleles or functional variants of these polymorphisms for individual drug metabolizing genes are defined with a "star" (*) designation. A combination of two *alleles, for example, *CYP2D6*1/*1*, is used to classify individuals into several genetically defined metabolic phenotypes with different expressions of enzyme activity. In general, the poor metabolizers (PMs) inherit two defective or deleted alleles and exhibit abolished-enzyme activity; the intermediate metabolizers (IMs) carry either one functional and one defective allele, or two partially defective alleles, and, in both cases, have reduced activity of the enzyme. The normal metabolizers are typically known as the extensive metabolizers (EMs) with two functional alleles and normal enzyme activity; and the ultrarapid metabolizers (UMs) carry a duplicated or amplified gene variant, resulting in two or multiple copies of the functional allele and very high enzyme activity.

In general, the clinical consequences of genetically altered-enzyme activity would depend on whether the pharmacological activity resides with the parent compound or the metabolite, and the relative contribution of the polymorphic isoenzyme to the overall metabolism of the drug. For the majority of the drugs, PMs would exhibit a higher risk of adverse drug reactions (ADRs), whereas UMs would experience lower efficacy when administered standard-dosage regimen of a drug that is mostly dependent on the polymorphic enzyme for elimination. In the case of a prodrug, the UMs exhibit higher incidence of ADRs, and the PMs experience lower efficacy, reflecting a difference in the extent of therapeutically active metabolite formed between the two metabolic genotypes.

Among the different *CYP* gene polymorphisms, those affecting CYP2D6, CYP2C19, and CYP2C9 are currently the most relevant with also the most abundant data, as well as representing most of the revised regulatory labeling information. Their potential role in translating the expanding pharmacogenomic knowledge into dose requirements and therapeutic decisions will be discussed first. An overview of the other major CYP isoenzymes will also be presented.

CYP2D6

CYP2D6 is the only drug-metabolizing CYP enzyme that is not inducible, and the significant interindividual differences in enzyme activity are largely attributed to genetic variations. *CYP2D6* is located on chromosome 22 and consists of 4382 nucleotides. The *CYP2D6* gene, which codes for the CYP2D6 enzyme, is composed of 497 amino acids. In addition, the *CYP2D6* gene polymorphisms are also the best characterized among all of the *CYP* variants, with at least 100 alleles identified. Nevertheless, Sistonen et al. [7] demonstrated that, even with the extensive number of alleles, determining 20 different haplotypes by genotyping 12 SNPs could predict the real phenotype with 90%–95% accuracy.

Among the multiple *CYP2D6* alleles, *CYP2D6*1*, *CYP2D6*2*, *CYP2D6*33*, and *CYP2D6*35* are active alleles with normal enzyme activity, whereas the two most

important null variants are *CYP2D6*4* (c.1846G>A, rs3892097) and *CYP2D6*5* (gene deletion), resulting in an inactive enzyme and absence of enzyme, respectively. Significant reduction in enzyme activity is commonly associated with *CYP2D6*10* (c.100C>T, rs1065852), *CYP2D6*17* (c.1023C>T, rs28371706, c.2850C>T, rs16947), and *CYP2D6*41* (c.2988G>A, rs28371725), and phenotypically expressed as IM. In addition, to these reduced function alleles, the IM phenotype has also been associated with the *CYP2D6*9*, **29*, and **36* variants [5]. Additional loss-of-function alleles include *CYP2D6*3*, **6–*8*, **11–*16*, **19–*21*, **38*, **40*, and **42*. CYP2D6 is also the first CYP isoenzyme for which CNVs were reported [8]. Individuals carrying up to 13 functional copies of the *CYP2D6*2* allele [9] have been reported to exhibit variation in response to different drugs [10,11]. After these initial reports, gene duplication has also been documented for the *CYP2D6*1*, **4*, **6*, **10*, **17*, **29*, **35*, **41*, **43*, and **45* variants [12]. Therefore, although UMs can result from duplication or multiduplication of the active CYP2D6 gene, duplication of partially functional and nonfunctional genes can also occur, resulting in different levels of gene expression and phenotypes of metabolic importance (Table 1.1). A CYP activity score has also been recommended for use in classifying the different 2D6 phenotypic groups [13]. More recently, a software tool (originally named "Constellation" and subsequently renamed as "Astrolabe") capable of allowing rapid, automated phenotype assignment has been made available for academic research at no cost [14].

Significant interethnic variations in *CYP2D6* allele and phenotype distributions have also been well documented. The normal function *CYP2D6*2* has been reported in approximately 25% of Caucasians, 31% of Africans, and 10%–12% of East Asians [15]. *CYP2D6*4* and *CYP2D6*5* (allelic frequency of about 20%–25% and 4%–6%, respectively) are predominantly found in Caucasian PMs, whereas the predominant variants in people of Asian and African heritage are *CYP2D6*10* (allelic frequency of about 50%) and *CYP2D6*17* (allelic frequency of about 20%–34%), respectively, both resulting in the IM phenotype. Therefore, even though the classic PM phenotypic frequencies determined

TABLE 1.1 Functional CYP2D6 Polymorphisms, Expected Enzyme Activity, and Predicted Metabolic Phenotypes for Selected Common Variants

Allelic Variants and Polymorphism	Functional Effect on Enzyme Activity	Predicted Metabolic Phenotypes
Active: **1, *2, *2A, *33, *35*	Normal activity	Extensive metabolizers: • Homozygous carriers of two active alleles • Heterozygous carriers of an active and a partially active allele
Partially active: **9, *10* (P34S), **17* (T107I, R296C), **29, *36, *41* (splicing defect)	Reduced activity	Intermediate metabolizers: • Heterozygous carriers of an active and a loss-of-function allele • Homozygous carriers of two reduced activity alleles • Heterozygous carriers of a partially active allele and a loss-of-function allele
Inactive: **3 (frame shift) *4 (splicing defect), *5 (gene deletion) *6 (frame shift), *7, *8, *11, *12, *13, *14, *15, *16, *19, *20, *21, *38, *40, *42* Gene duplication have been reported for both **4* and **6*	Loss-of-function	Poor metabolizers: • Homozygous carriers of two loss-of-function alleles
Gene duplications/copy number variants **1, *2, *10, *17, *29, *35, *41, *43, *45*	Enhanced activity	Ultrarapid metabolizers: • Carriers of ≥3 active alleles

in Asians (about 0%–1% of population) and Africans (0%–5% of population) are lower than that reported for the Caucasians (5%–14% of population), the high prevalence of *CYP2D6*10* and *CYP2D6*17* in these two IM populations provides a biologic and molecular explanation for reported higher drug concentrations and/or the practice of prescribing lower dosage requirements in people of Asian and African heritage [16–19]. On the other hand, the UM phenotypic frequency is much higher in Northeast Africa and Oceania, including the Saudi Arabian (20%) and black Ethiopian (29%) populations when compared to Caucasians (1%–10%) and East Asians (0%–2%).

Even though accounting for a small percent of total CYP content in the liver, CYP2D6 mediates the metabolism of approximately 20%–30% of currently marketed drugs, and *CYP2D6* polymorphism affects significantly the elimination of 50% of these drugs [20], which include antidepressants, antipsychotics, analgesics, antiarrhythmics, antiemetics, and anticancer drugs. Although differences in pharmacokinetic parameters (elimination half-lives, clearances, and areas under the plasma concentration–time curves) for CYP2D6 substrates could be demonstrated among the different metabolic phenotypes, the significant overlap in CYP2D6 activities in EMs and IMs result in therapeutic implication mostly for the PM and UM phenotypes. In the past, the clinical relevance of *CYP2D6* polymorphism primarily concerned the increased prevalence of ADRs in PMs administered standard doses of drugs that rely significantly on CYP2D6 for elimination. These drugs include the antianginal agent perhexiline (neuropathy) [21], the antiarrhythmic agent propafenone (proarrhythmic events) [22], and neuroleptic agents such as perphenazine (sedation and parkinsonism) [23,24].

More recently, occurrences of ADRs have also been highlighted in UMs, primarily a result of a 10–30-fold increase in metabolite concentrations. The most cited example is that of codeine, which is converted by CYP2D6 to the pharmacologically more active metabolite morphine. UMs administered the usual therapeutic dose of codeine have been reported to exhibit symptoms of narcotic overdose associated with significantly elevated morphine concentrations. This toxicity potential had been highlighted in several case reports [25–29], including a fatal case of a breast-fed infant that was attributed to extensive formation of morphine from codeine taken by the mother who is a UM [26]. (Table 1.2) Prior to this unfortunate case, codeine has been considered safe for managing pain associated with childbirth, as literature reported low amounts of codeine are usually found in breast milk. Therefore, this fatal case underscores the importance of understanding how genes can affect pharmacological and therapeutic outcome associated with exposure to drug and/or active metabolite.

Given the high incidence of codeine use in postgestational women, Madadi et al. subsequently performed a case-control study in breast-fed infants with or without central nervous system depression signs and symptoms after exposed to codeine during breast feedings. They reported that breast-fed infants from mothers who are CYP2D6 UMs and homozygous carriers of *UGT2B7*2* (rs7439366; UGT2B7 is a phase 2 enzyme involved in codeine glucuronidation) have an increased risk of potentially life-threatening central nervous system depression [30]. Since 2007, the Food and Drug Administration (FDA) had issued several warning in revised prescribing information for codeine label. Citing the risk of morphine overdose in children and breast-fed infants and warnings from the FDA, the World Health organization, Health Canada, and the European Medicine Agency, the Academy of Pediatrics had recently cautioned the use of codeine in children, regardless of age [31].

Samer et al. reported higher incidence of oxycodone toxicity in UMs that could be partially related to CYP2D6-mediated metabolism to oxymorphone. The toxicity incidence is especially higher in those with concurrent

TABLE 1.2 Summary of Selected Literature on Impact of CYP2D6 Genotype and/or Drug Interaction on Opioid Safety

	Allelic Variants Reported	Adverse Events	References
Codeine	*CYP2D6*1* ×3	Life-threatening opioid intoxication exacerbated by drug interaction (with erythromycin and voriconazole) and renal insufficiency	[25]
	*CYP2D6*2A/*2*×2	Fatality in a breast-fed baby whose mother is a UM	[26]
	*CYP2D6*1* ×N	Fatality in a two-yr-old child due to respiratory arrest	[27]
	CYP2D6 ×2	Occurrence of apnea and brain injury in a 29-mo old child	[28]
	CYP2D6 gene duplication *CYP2D6*1* ×N	Fatality in two children who are UMs. Respiratory depression in an CYP2D6 EM who survived	[29]
Hydrocodone	*CYP2D6*2A/*41*	Fatality in a child who also received concurrent clarithromycin	[33]
Oxycodone	CYP2D6 UMs	Greater toxicity, especially in those administered ketoconazole	[32]
Tramadol	Heterozygous carrier of a wild-type allele duplication	22-yr with a near-fatal case of cardiac arrest and high concentration of tramadol metabolite	[34]
	CYP2D6 gene duplication	Tramadol-related respiratory depression	[35]

ketoconazole administration [32]. Similarly, drug interaction with clarithromycin might have played a role in the fatal case after hydrocodone exposure experienced by a 5-yr-old developmentally delayed child with a *CYP2D6*2A/*41* genotype [33]. In addition, tramadol cardiotoxicity and respiratory depression have been reported in UMs [34,35] with high level of the active O-desmethyltramadol [34], which has been reported to exhibit a high correlation with increased plasma epinephrine level [36]. The FDA also recently updated its safety warning for tramadol.

In addition to implications for ADR, the efficacy of prodrugs (such as codeine and hydrocodone) would also be reduced in PMs because less parent drug is converted by CYP2D6 to its respective active metabolite: morphine or hydromorphone, resulting in little analgesic relief [37]. However, despite strong evidence of a genotype effect on the pharmacokinetics of codeine and hydrocodone, the impact on dosage requirement is much less obvious. In this regard, the value of CYP2D6 genotype lies more with guiding the choice of the appropriate analgesic rather than genotype-based dosage recommendation [13,38]. In particular, avoidance of codeine, the only opioid analgesic with a Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, is recommended for PMs and UMs. In addition, hydrocodone may not be a good alternative analgesic agent to codeine in these patient populations [13].

There are similar reports of lower efficacy in PMs with venlafaxine [39]. Another example is tamoxifen, in which CYP2D6 plays a major role in the formation of the abundant and pharmacologically more active metabolite, endoxifen [40]. Because endoxifen possesses greater affinity for the estrogen receptor than tamoxifen, PMs with the *CYP2D6*4/*4* genotype have been shown to have an increased risk of breast cancer recurrence and worse relapse-free survival, as well as a much lower incidence of moderate or severe hot flashes [40]. The results of Kiyotani et al. [41] showed that the association between tamoxifen

response and CYP2D6 genotype in Japanese breast cancer patients was only evident for those patients receiving tamoxifen monotherapy, and underscores the importance of considering concomitant drug therapy in pharmacogenomics association study with tamoxifen and possibly other drugs. Conflicting data and continued debate complicate the adoption of CYP2D6 genotyping in the therapeutic use of tamoxifen currently for patients with estrogen-receptor positive breast cancer. Nevertheless, available evidence strongly supports a role for CYP2D6 in pharmacological activation of tamoxifen [42] and possibly a likelihood of lesser therapeutic benefit in PMs [43], with the ultimate impact on patient outcome to be tested in prospective clinical studies.

Inadequate therapeutic response with implications for dosage adjustment had also been demonstrated for UMs administered CYP2D6 substrates. The best evidence described two patients with multiple copies of *CYP2D6*2* requiring the tricyclic antidepressant nortriptyline 500 mg daily (vs. usual recommended daily dose of 100–150 mg) in one patient [44] and clomipramine 300 mg/day (vs. 25–150 mg) in another patient [9] to achieve adequate therapeutic response. Similarly, lower efficacy in UMs has been reported with other antidepressants [45,46] and antiemetics such as ondansetron [47].

Nevertheless, the therapeutic significance of CYP2D6 is not only impacted by genetic polymorphism but also by the potential of CYP2D6-mediated drug–drug interaction, with clinical implications in patients with different metabolic phenotypes resulting from competitive inhibition of CYP2D6. As shown by Hamelin and colleagues [48], the pharmacological consequences of drug–drug interaction via CYP2D6 inhibition are of greater magnitude in EMs, with pronounced and prolonged hemodynamic responses to metoprolol, than in PM.

Potent CYP2D6 inhibitors had been shown to reduce the metabolic capacity of EMs significantly so that individual EM could appear *metabolically* as PM during concurrent administration [49] which could have therapeutic significance in patients taking multiple drugs. For example, it is not uncommon that tamoxifen-treated patients are also taking antidepressants such as selective serotonin reuptake inhibitors (SSRIs), for both their antidepressant effect as well as their offlabel use to manage hot flashes. In view of the abundance and greater antiestrogenic activity of endoxifen, concurrent administration of SSRIs that are potent inhibitors of CYP2D6 (such as fluoxetine and paroxetine) should best be avoided, and SSRIs with a lesser extent of CYP2D6 inhibition (such as citalopram and venlafaxine) would be better alternate antidepressants if there is a need for concurrent antidepressant therapy with tamoxifen.

Interestingly, Gryn et al. described significant reduction in endoxifen concentration in a patient with *CYP2D6*1/*41* genotype. The reported endoxifen concentration was described as "well below levels seen in most CYP2D6 poor metabolizers." Although the case report did not investigate the mechanism for the altered level, the authors suggested it could be secondary to the patient's concurrent treatment with phenytoin. Phenytoin is a potent inducer of multiple drug-metabolizing enzymes as well as the efflux drug-transporter ABCB1 (also known as multidrug resistance transporter, and described in more details in later sections) [50], which mediates the efflux transport of endoxifen [51]. Although the clinical outcome was not described, this case underscores the importance of evaluating the modulating effect of drug interaction when utilizing genotyping in individualized therapy [52]. Similar modulating effects on other genes encoding different metabolizing enzymes are described in later sections.

In addition, it is important to realize that the potential for drug interaction via CYP2D6 inhibition could also be affected by the basal metabolic activity of the individual patient. We have shown that the UM phenotype could affect the potential for drug interaction with paroxetine, a

CYP2D6 substrate as well as a potent CYP2D6 inhibitor, whence a UM with three functional *CYP2D6* copies had undetectable paroxetine concentration with standard dosing and showed no inhibitory effect at CYP2D6 [53].

CYP2C19

CYP2C19 is located on chromosome 10q23.33 and is a large gene consisting of 90,209 nucleotides and yet coding for CYP2C19 that contains only 490 amino acids. Compared to the *CYP2D6* polymorphism, polymorphisms in the *CYP2C19* gene do not affect as many drugs, and their clinical implication has not been extensively evaluated. However, studies involving the proton pump inhibitors (PPIs) provide extensive pharmacokinetic and clinical evidence, as well as the economic impact of the importance of taking into consideration of *CYP2C19* polymorphism in the management of gastroesophageal diseases.

Over the years, as many as 30 *CYP2C19* alleles, including those with no functional activity (**2, *3, *4, *6, *7)* and those associated with reduced catalytic activity (**5* and **8*), have been identified (www.cypalleles.ki.se/cyp2c19.htm). The principal null alleles are **2* (c.681G>A, rs4244285) and **3* (c.636 G>A, rs4986893), resulting in an inactive CYP2C19 enzyme, and accounting for the vast majority of the PM phenotype in Caucasians (1%–6%), black Africans (1%–7.5%), and Asians (10%–25%). Genotyping these two defective alleles has been shown to detect about 84%, greater than 90%, and about 100%, of PMs in Caucasians, Africans, and Asians, respectively. The detection rate for Caucasians PMs could be increased to about 92% by including the less common *CYP2C19*4* (rs28399504) and *CYP2C19*6* (rs72552267) in the genotyping assay. Similar to other *CYP2C19* rare variants, **5* (rs56337013), **7* (rs72558186), and **8* (rs41291556) have <1% allele frequency. Individuals carrying at least one functional allele are referred as EMs, whereas those with one functional and one loss-of-function allele are IMs. Of interest is that, similar to *CYP2D6* polymorphism, a "gain of function" *CYP2C19*17* allele (c.-806C>T rs12248560) was identified in the 5′-flanking region of *CYP2C19*, with increased gene transcription associated with high enzyme activity and an EM phenotype [54].

*CYP2C19*2* and **3* are commonly found in Asians, with allele frequencies of about 30% and approximately 10%, respectively. In contrast, the allele frequency of **3* is <1% in Caucasians and African Americans, even though the **2* occurs at a frequency of about 13% and approximately 18%, respectively, in these two ethnic groups. About 50% of the Chinese population possess either the **1/*2* and **1/*3* genotypes, and 24% have the **2/*2*, **2/*3*, or **3/*3* genotypes [55]. In contrast, only about 2%–5% and 30%–40% of the Caucasian population, respectively, have the **2/*2* and **1/*2* genotypes. Similar frequencies of the heterozygous and homozygous variant genotypes are reported in persons of African descent. The higher prevalence of PMs and heterozygote EMs carrying defective *CYP2C19* alleles in Asians likely account for reports of slower rates of metabolism of CYP2C19 substrates and the practice of prescribing lower diazepam dosages for patients of Chinese heritage [56,57]. An opposite direction in ethnic variation was observed in the prevalence of *CYP2C19*17* (18% in Swedes and Ethiopians vs. 4% in Chinese), with the **1/*17* and **17/*17* genotypes occurring in more Caucasians and Ethiopians (up to 36%) than Asians (8% of Chinese and 1% of Japanese) [54].

CYP2C19 accounts for about 3% of total hepatic CYP content, and *CYP2C19* polymorphism affects the metabolism of PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole), antidepressants (citalopram, sertraline, moclobemide, amitriptyline, clomipramine), the antiplatelet agent clopidogrel, the antifungal drug voriconazole, the benzodiazepine diazepam, and the anticancer drug cyclophosphamide. Similar to CYP2D6, CYP2C19 is also susceptible to inhibition by drugs such as cimetidine, fluoxetine, and diazepam. The inhibition occurs in a gene

dose-dependent manner in which carriers of two *CYP2C19*17* alleles exhibit the greatest extent of inhibition compared to little to no inhibition for patients with CYP2C19 PM phenotype.

The PPIs and clopidogrel provide the best examples of clinical relevance of *CYP2C19* polymorphism. When compared to EMs, PMs showed 5- to 12-fold increases in the area under the curve (AUC) of omeprazole, lanzoprazole, and pantoprazole [58,59], whereas homozygous carriers of the *CYP2C19*17* were shown to have a modest 2.1-fold lower AUC than EMs [60]. In addition, the *CYP2C19* genotype significantly affects the achievable intragastric pH with PPI therapy. In subjects who took a single 20-mg dose of omeprazole, Furuta et al. showed a good relationship not only between *CYP2C19* genotype and AUC, but also between the genotype and achievable intragastric pH: 4.5 in PMs, 3.3 in heterozygous EMs, and 2.1 in homozygous EMs [61]. Given the smaller dependency of esomeprazole and rabeprazole on CYP2C19 for metabolism, the pharmacological action of these two PPIs is less affected by the *CYP2C19* polymorphism [62,63].

An important treatment strategy in the management of patients with peptic ulcer disease is eradication of *Helicobacter pylori* with a regimen of PPI and antibiotics. *CYP2C19* genotype-related pharmacological effects have also been associated with improved eradication rate of *H. pylori* after dual [64] or triple therapy including omeprazole [65], lansoprazole [66], or pantoprazole [67]. The cure rate achieved with dual- and triple-therapy regimens was 100% in PMs compared with 29%–84% in EMs [64–67]. Furata et al. also reported a much higher eradication rate of 97% in EMs who failed initial triple therapy (lansoprazole, clarithromycin, and amoxicillin) and subsequently were retreated with high-dose lansoprazole (30 mg four times daily) and amoxicillin [68]. In addition, to showing a gene-dose effect in achieving desirable ranges of intragastric pH and *H. pylori* cure rates for lansoprazole, Furuta et al. also demonstrated the cost effectiveness of pharmacogenomics-guided dosing when compared to conventional dosing [69]. On the other hand, despite increased metabolism of PPI in carriers of *CYP2C19*17* and the potential of therapeutic failure [54,70], eradication rates of *H. pylori* have so far not to be shown to be associated with the *CYP2C19*17* allele, at least for patients with peptic ulcer disease and receiving the triple regimen of pantoprazole, amoxicillin, and metronidazole [67,71].

In healthy volunteers given a single 200-mg dose of voriconazole, Wang et al. demonstrated a 48% lower AUC in heterozygous carriers of the *CYP2C19*17* allele as compared to homozygous carriers of *CYP2C19*1* [72]. This finding is consistent with data that is more recent showing correlation between *CYP2C19* polymorphism and target voriconazole concentrations, with an increased risk of subtherapeutic trough concentration in patients with the CYP2C19 UM phenotype [73–75]. Investigators have also shown 42% lower escitalopram concentrations and 21% lower AUC in patients who are homozygous carriers of *CYP2C19*17* when compared to *CYP2C19*1* homozygotes [76]. Clearly, *CYP2C19*17* homozygotes might require higher doses of most CYP2C19 substrates, including PPIs [60,70], antidepressants, and voriconazole [72]. However, despite the presence of pharmacokinetic differences, the impact of *CYP2C19*17* on therapeutic outcomes with these CYP2C19 substrates have not been evaluated extensively or confirmed.

Clopidogrel is an antiplatelet prodrug that requires CYP2C19-mediated conversion to its active metabolite for therapeutic effect [77], with most of pharmacokinetic and pharmacodynamic evidence related to the *CYP2C19*2* allele [77–82]. Shuldiner et al. conducted a GWAS in which *ex vivo* adenosine diphosphate (ADP)-induced platelet aggregation at baseline and after 7 days of clopidogrel were measured in a genetically homogenous cohort of 429 healthy Amish subjects. In addition, 400,230 SNPs were evaluated in each subject for association with

platelet activity. They reported that the SNP rs12777823 on chromosome 10q24 with the greatest association signal is in strong LD with *CYP2C19*2*, accounting for 12% of the interindividual variation in platelet aggregation during clopidogrel treatment. As importantly, there was no association between the *CYP2C19* polymorphism and baseline platelet aggregation [83]. The results from this GWAS confirmed results from previous candidate gene studies regarding the role of *CYP2C19* as a major genetic determinant of clopidogrel response [78–82]. In a follow-up study of 227 patients undergoing percutaneous coronary intervention (PCI), the investigators also reported a higher incidence of cardiovascular death in carriers of the *2 allele (20.9% vs. 10%) at 1-yr follow-up. No association with response was found for other *CYP2C19* alleles, including *3, *5* (rs56337013), and *17*, that were also genotyped in the study [83]. A recent meta-analysis confirms the association of the *CYP2C19* nonfunctional allele and high-risk of adverse cardiovascular events in patients who underwent PCI [84].

Although the increased production of the active clopidogrel metabolite in carriers of the *17* allele has been associated with greater inhibition of platelet aggregation [85,86] and better clinical outcomes [87], there is also the potential of increased bleeding risk [88]. In addition, the increased response of the *17* allele has been suggested not as a direct effect, but rather attributed to that of the *1* allele [89]. Given this consideration, there is no specific therapeutic recommendation for this gain-of-function allele in the most recent practice guideline for *CYP2C19* genotyping [90].

Even with involvement of other non-genetic factors [91], the increased risks of major adverse cardiovascular events and stent thrombosis in carriers of at least one *CYP2C19*2* allele were confirmed in two meta-analyses that included almost 22,000 patients [88,92]. Differences in patient selection for analysis likely account for the lack of association reported in two other recent meta-analyses, which included a significant number of low-risk patients, such as those with acute coronary syndrome managed medically or patients with atrial fibrillation [93,94]. The meta-analysis of Hulot et al. [92] also evaluated the drug interaction potential of PPIs because of their inhibitory effect toward CYP2C19, resulting in a metabolic phenotype of CYP2C19 PM similar to that of carriers of the *2 allele. Both Hulot et al. and another study [92,95] suggest that the detrimental effects of PPIs on cardiovascular outcomes with clopidogrel likely occur at a higher frequency in high-risk patients receiving both drugs. Current data do not provide sufficient information to determine whether the observed adverse effects of PPI usage in high-risk patients (e.g., patients undergoing PCI) are related to CYP2C19 inhibition or yet-to-be-discovered mechanisms.

Based on the increasing amount of literature data supporting an association between *CYP2C19*2* and poor clopidogrel response, the FDA has made several revisions to the approved product label of clopidogrel. Although the March 2010 version specifically addresses the implication for homozygotes, there is no guidance on the implication for heterozygotes. In addition, as with other revised labels with additional genetic information, there is little guidance on clinical management of carriers of *CYP2C19*2*. The September 2016 label warns of diminished effectiveness in CYP2C19 poor metabolizers and suggests the use of different platelet P2Y12 inhibitors in those patients. In light of the scientific and clinical evidences as well as the regulatory decision, several recent clinical studies addressing alternative antiplatelet agents have been initiated and are discussed in Chapter 6.

CYP2C9

In addition to CYP2C19, another important member of the CYP2C subfamily of enzymes is CYP2C9 containing 490 amino acids. It is encoded by *CYP2C9* consisting of 50,708 nucleotides and located on chromosome 10q24.1 in close

proximity to *CYP2C19*. To date, approximately 60 *CYP2C9* alleles (www.cypalleles.ki.se/cyp2c9.htm) have been identified in the regulatory and coding regions of *CYP2C9*, with *CYP2C9*2* (c.430C>T, rs1799853) and *CYP2C9*3* (c.1075A>C, rs1057910) being the most common in persons of European descent and the most extensively studied. Both reduced-function alleles exhibit single amino-acid substitutions (p.R144C and p.I359L, respectively) in the coding region, accounting for lower enzyme activity by approximately 30% for *2 and 80% for *3 [96]. Other reduced-function alleles of potential importance included *5 (rs28371686), *6 (rs9332131), *8 (rs7900194), and *11 (rs28371685). [97–100] In addition, a "gain-of-function" *CYP2C9* (rs7089580) variant in intron 3 has been identified [97].

Significant variations in *CYP2C9* alleles and genotype frequencies exist among different ancestry groups. Both *CYP2C9*2* and *CYP2C9*3* are more common in Caucasians (11% and 7%, respectively) than in Asians and Africans. In fact, *CYP2C9*2* has not been detected in Asians, in whom *CYP2C9*3* is the most common allele. On the other hand, *CYP2C9*8*, as well as *5, *6, and *11 (albeit all at a lower frequency than *8*), are present almost exclusively in African Americans. The novel *CYP2C9* c.18786A>T variant (rs7089580) was reported to occur in about 40% of the African American population, and *CYP2C9*8* (c.449G>A, rs7900194) appears to be a major contributor to CYP2C9 expression in this ethnic group [97]. Approximately 1% and 0.4% of Caucasians have the *2/*2 and *3/*3 genotypes, respectively. The *1/*3 genotype occurs at a frequency of 4% in the Chinese and Japanese populations, with almost complete absence of the other genotypes (*2/*2, *2/*3, *1/*2, and *3/*3).

CYP2C9 accounts for about 20% of total hepatic CYP content and is involved in the metabolism of about 10% of currently marketed drugs. These CYP2C9 substrates include the nonsteroidal antiinflammatory drugs such as celecoxib, ibuprofen, and flurbiprofen; oral anticoagulants such as acenocoumarol, and phenprocoumon, and the S-isomer of warfarin; oral antidiabetic agents such as glibenclamide, glimepiride, glipizide, glyburide and tolbutamide; antiepileptic agents such as phenytoin, and antihypertensive agents such as candesartan, irbesartan, and losartan. The enzyme reduction associated with the *3 allele is greater than that with the *2 allele, with a 5- to 10-fold reduction in homozygous *3 carriers and two-fold reduction in heterozygous *3 carriers, when compared to homozygous *1 carriers. For example, clearance of warfarin is reduced by 90%, 75%, and 40% in subjects with the corresponding *CYP2C9* genotypes of *3/*3, *1/*3, and *1/*2 [101]. respectively. Interestingly, the effects of several reduced-function alleles appear to be substrate dependent. For the *2 allele, a significant effect was shown for clearances of acenocoumarol, tolbutamide, and warfarin but not for other substrates. On the other hand, nonsteroidal anti-inflammatory drug (NSAID)-associated gastrointestinal bleeding was shown to be related to the *3 but not the *2 variant [102]. Similarly, although the *8 allele has no effect on clearance of losartan, it decreases enzyme activity of warfarin and phenytoin, and exhibits an increased activity toward tolbutamide [103].

Of all of the CYP2C9 substrates, warfarin is the most extensively studied with dosing implications for different metabolic phenotypes. *CYP2C9* polymorphism, together with the literature information regarding the gene that encodes the warfarin target, vitamin K epoxide reductase complex (VKORC1) [104], provide promising translational use of the pharmacogenomic data [105,106], with revised language regarding their impact incorporated into the drug label [107]. CYP2C9 mediates the conversion of the active *S*-enantiomer of warfarin to an inactive metabolite. Most of the data document that the *2 and *3 alleles are associated with greater difficulty with warfarin induction therapy, increased time to achieve stable dosing, lower mean-dose requirement (e.g., as low as ≤1.5 mg/day with *3/*3), as well as increased risks of elevated , international normalized ratios (INRs) and bleeding [105,108,109]. Giving the 30%

and 80% difference in enzyme activity reduction between the *2 and *3 alleles, the warfarin-dose requirements differ between carriers of these two alleles. Compared to homozygous carriers of the *1 allele, data suggest a dose reduction of 30% and 47% for patients with the heterozygous genotypes of *CYP2C9*1/*2* and *CYP2C9*1/*3*, respectively, and up to 80% for patients with the homozygous *CYP2C9*3/*3* genotype [106,108,110,111].

In addition, with the difference in allele prevalence among different ancestral groups, the strength of association between the *2 and *3 alleles and genotypes is stronger in Caucasians [112,113]. Other recently identified alleles (*5, *6, *8, and *11) have been reported to better predict dose requirement (20% lower for *8 carrier) and adverse outcomes in African Americans [97–99,103,112,114]. On the other hand, the "gain-of-function" *CYP2C9* c.18786A>T allele was reported to contribute a higher-dose requirement (3.7 mg/week/allele) [97]. Finally, concurrent drugs with significant modulating effect on CYP2C9 activity would also have an impact on the association between *CYP2C9* genotypes and warfarin-dose requirement [115]. The effect of *CYP4F2* and *VKORC1* genotypes on warfarin pharmacokinetics and pharmacodynamics will be discussed in later sections of this chapter.

CYP2C8

In addition to *CYP2C9* and *CYP2C19*, the other clinically relevant members of the highly homologous genes (*CYP2C18–CYP2C19–CYP2C9–CYP2C8*) that cluster on chromosome 10q24 [83] is *CYP2C8*. To date, several SNPs within the coding region of the *CYP2C8* gene have been identified (www.cypalleles.ki.se/cyp2c8.htm). The more common variants are *2 (c.805A> T, rs11572103, resulting in p.I269F), *3 with two amino acid substitutions (c.416G >A, rs11572080 with p.R139K, and c.1196A >G, rs10509681 with p.K399R) reportedly to be in total LD, and *4 (c.792C >G, rs1058930, p.I264M). Both *3 and *4 alleles are more common in Caucasians (with the *4 variant reportedly only found in Caucasians). On the other hand, *2 and a rare allele, *5 (rs72558196, frame-shift deletion) are exclusively found in Africans and Japanese, respectively [116,117].

Accounting for about 7% of total hepatic content, the hepatic expression level of CYP2C8 lies between that of CYP2C19 and CYP2C9 [118], and it plays an important role in the metabolism of different drugs, primarily the antidiabetic agents (pioglitazone, repaglinide, rosiglitazone, and troglitazone), the anticancer agents (paclitaxel), the antiarrhythmic drug amiodarone, and the antimalarial agents amodiaquine and chloroquine. The smaller number of substrates as compared to CYP2C9 and CYP2C19 presumably leads to the lesser interest in studying *CYP2C8* polymorphism. As a result, the molecular mechanisms underlying interindividual variations in CYP2C8 activity remain unclear. Decreased elimination of R-ibuprofen has been reported in carriers of *CYP2C8*3* [119,120]. However, with the presence of a strong LD between *CYP2C8*3* and *CYP2C9*2* [119,121], the individual contribution of *CYP2C8*3* remains to be elucidated. In contrast, increased metabolism of repaglinide was reported in heterozygous carriers of *CYP2C8*3* when compared to carriers of either *1 or *4 [122]. Although this finding is interesting, other reports showed that genetic polymorphism of the hepatic uptake transporter plays a more important role in determining repaglinide pharmacokinetics [123]. The identification of two *CYP2C8* haplotypes: a high-activity allele associated with *CYP2C8*1B* and a low activity associated with *CYP2C8*4* [124], further highlights the need to characterize the different *CYP2C8* variants, including their functional relevance.

CYP3A4/5/7

A total of four CYP3A genes have been described in humans: *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*; with *CYP3A7* primarily important in fetal CYP3A metabolism and

CYP3A43 exhibiting little functional or clinical relevance. More than 20 variants in the coding region of *CYP3A4*, most of them associated with reduced catalytic activity of the enzyme, have been identified to date. [125] The significance of the reduced-function allele *CYP3A4*22* C>T SNP (rs35599367) in intron 6, which results in 20% decrease in enzyme activity, has been extensively evaluated recently, especially in conjunction with *CYP3A5* SNP [126–129]. *CYP3A5* expression is highly polymorphic with the loss-of-function **3* allele (c.6986A>G, rs776746) in intron 3 as the most common variant, which results in a splicing defect and absence of enzyme activity. Other loss-of-function and reduced-function *CYP3A5* variants include the **2* (rs28365083; g.27289C>A; T398N), **6* (14690G>A; rs10264272), and **7* (rs41303343; 27131_27132ins T) alleles [130,131].

In general, *CYP3A4* polymorphism is more common in Caucasians, with **2* and **7* being the more prevalent alleles, whereas Asians have higher frequencies of **16* and **18* variants. Of note, is that *CYP3A4*22* is absent in both Asian and African populations. Carriers of the wild-type *CYP3A5*1* allele (also known as CYP3A5 "expressors") are more common in Asians (up to 50%) and Blacks (up to 90%) than in Caucasians (about 15%). The allele frequency of *CYP3A5*3* is much higher in Caucasians and Asians, occurring in 90% and 75% of the populations, respectively, *versus* a relatively low frequency of 20% in Africans. On the other hand, both *CYP3A5*6* and **7* are absent in Caucasians and Asians but present in Africans with frequencies up to 17% [130,132,133]. The *CYP3A5*2* allele has a frequency of less than 1% in Caucasians and is mostly absent in other ethnic populations.

CYP3A4 accounts for about 40% of the total hepatic CYP content and mediates the metabolism of more than 50% of currently used drugs with many examples from the pharmacological classes of macrolide antibiotics, antidepressants, antipsychotics, anxiolytics, calcium channel blockers, immunosuppressants, opiates, and the statins. The current consensus is that *CYP3A4* polymorphisms are mostly of minor clinical relevance, and unlikely responsible for the 10- to 40-fold interindividual variations in CYP3A4 activities. This is likely a result of low variant allele frequencies, only small changes in enzyme activity in the presence of a variant allele, as well as the overlapping substrate specificity between CYP3A4 and CYP3A5. The significant variability in CYP3A4 activity is more likely related to a large number of drugs capable of altering the enzyme through induction or inhibition in the liver and the gastrointestinal tract. Therefore, there is currently no uniform agreement on metabolizer subgroups for CYP3A4.

On the other hand, the clinical relevance of CYP3A genetic polymorphism is primarily associated with *CYP3A5*. The pharmacokinetics of the immunosuppressive agent tacrolimus is dependent on the *CYP3A5* genotype, with a higher-dosage requirement in homozygous or heterozygous carriers of *CYP3A5*1* [134,135]. In addition, results from a randomized controlled trial showed that pharmacogenetic-guided dosing based on *CYP3A5* genotype was associated with greater achievement of target tacrolimus concentrations when compared to standard dosing based on body weight [136]. Nevertheless, the overall clinical relevance of *CYP3A5* polymorphism is limited by its small contribution (2%–3%) to the total CYP3A metabolism. [137,138], and reportedly impacted by timing of tacrolimus therapy. In a meta-analysis of tacrolimus-dose requirement and rejection rate, Tang et al. indicated that the effect of *CYP3A5* polymorphism (*CYP3A5*3*) is most prominent during the first month of tacrolimus therapy, suggesting that *CYP3A5* genotyping might be useful to guide initial dosing of tacrolimus for prevention of early graft rejection [139]. Inclusion of both *CYP3A4*22* and *CYP3A5*3* status have been shown in many recent studies to significantly improve tacrolimus dose prediction [126–129,140]. Therapeutic and pharmacogenomic recommendations for tactolimus were included in the recent CPIC guideline [141].

On the other hand, despite significant effect of *CYP3A4*1G* (g.20230G>A, rs2242480) and *CYP3A5*3* on ticagrelor pharmacokinetics in a recent study of healthy Chinese subjects, there was no association on the extent of inhibition of platelet aggregation. Therefore, the investigators concluded that no dosage adjustment based on *CYP3A4* and *CYP3A5* genotypes is necessary [142].

CYP4F2

There are six members within the *CYP4F* gene subfamily residing on chromosome 19p13.1-2: *CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12*, and *CYP4F22*. The importance of CYP4F2, a vitamin-K oxidase, is related to the recent report of its role in mediating the conversion of vitamin K_1 to hydroxyvitamin K_1. Increased CYP4F2 activity causes decreased activation of vitamin K-dependent clotting factors, reflecting the consequence of reduced availability and reduction of vitamin K_1 to vitamin KH_2 necessary for carboxylation and activation of the clotting factors. On the other hand, the g.7253233C>T (rs2108622, p.V433M) SNP in exon 2 of the *CYP4F2* gene results in lower protein expression and enzyme activity, and consequently greater vitamin K_1 availability [143,144]. The T allele at rs2108622 confers the *CYP4F2*3* designation. Some ethnic differences in the V433M SNP has been reported, with the M433 allele occurring at a much lower frequency in African Americans [114], which contrast with its high occurrence in Indonesians and Egyptians [145,146].

Although genome-wide association studies enable detection of weaker genetic signals [144], *CYP4F2* genotype nevertheless only accounts for 1%–3% of the overall variability of warfarin-dose requirement [144,147], in contrast to *CYP2C9* genotype that accounts for approximately 10%–12% of the variability. Homozygous carriers of the M allele of the p.V433M SNP had been shown to require an approximate 1 mg/day higher dose of warfarin than homozygous carriers of the V allele [148]. However, additional studies demonstrated the association between the *CYP4F2* genotypes and dose requirements in Caucasians and Asians [144,147,149,150] but not in African Americans, Egyptians, or Indonesians [114,145,146]. This could reflect ethnic differences in *CYP4F2* allele and genotype frequencies distribution, the minor contribution of *CYP4F2* [151], as well as the modulating effects of other more important dose-requirement variables such as *CYP2C9* and *VKORC1*.

CYP2B6

Although several variant alleles with low enzyme expression, including *CYP2B6*6* and **18*, have been identified, to date there have not been any reports of the presence of an important loss-of-function allele. Among the variant alleles, the *CYP2B6*6* haplotype carrying two nonsynonymous SNPs (c.516G>T, rs3745274 and c.785A>G, rs2279343 causing two amino acid changes: p.Q172H and p.K262R, respectively) in exon 4 is the most common and occurs commonly in Caucasians and Asians (16%–26% allele frequency), whereas**18* (c.983T>C, rs28399499, I328T) is more common in Black subjects with allele frequencies of 7%–9% [152]. Interestingly, the 785A>G SNP resulting in the K262R amino acid change also occurs as a separate allele, *CYP2B6*4* (rs2279343 without rs3745274), and results in increased expression and enzyme activity [153,154]. Whether the 516G>T and 785A>G mutations are linked to additional mutations creating specific haplotypes causing either high or low CYP2B6 activities is not known. Gatanaga et al. also reported a new **26* allele containing 499G for the c.499C>G SNP (rs3826711), and 499G always coexists with 516G>T and 785A>G, thus representing a novel haplotype containing the 499C>G, 516G>T and 785A>G SNPs [155].

CYP2B6 accounts for up to 6%–10% of total CYP content in the liver [156,157], and known substrates include anticancer drugs such as

cyclophosphamide and ifosfamide, the smoking cessation agent bupropion, the antiretroviral agents efavirenz and nevirapine, as well as methadone. In addition to reduced activation of cyclophosphamide leading to lower antitumor efficacy, *CYP2B6* gene variants play a significant role in determining bupropion and methadone pharmacokinetic variabilities, in particular with *CYP2B6*6* (decreased clearance) [158–160] and *CYP2B6*4* (increased clearance) [159]. Levran et al. reported that the mean daily methadone dose in heroin addicts was 88 and 96 mg, respectively, for homozygous carriers of variant alleles 785A>G and 516G>T; as compared to 133 and 129 mg, respectively, for heterozygous carriers of the two variant alleles; and 150 and 151 mg, respectively, for wild-type homozygotes [161]. In individuals whose death was attributed to methadone poisoning, *CYP2B6*4*, **6*, and **9* alleles were associated with higher postmortem methadone blood concentrations ($P \leq .05$) [162]. However, despite report of longer corrected QT interval (QTc) interval in CYP2B6 slow metabolizers [163], a clear relationship between *CYP2B6* genotype and risk of cardiac arrhythmia and sudden death remains to be determined.

The potential clinical relevance of CYP2B6 has been evaluated primarily with the nonnucleoside reverse transcriptase inhibitors efavirenz and nevirapine. Increased central nervous system side effects associated with variable systemic exposure of efavirenz could be the result of patients being carriers of the **6* or **18* alleles [155,164]. Incorporating determination of additional less-frequent alleles such as **26* and **29* could further improve the prediction of elevated plasma efavirenz concentrations [155,164,165]. Altered concentrations of, and clinical outcome associated with, nevirapine have also been associated with *CYP2B6* rs3745274 SNP.

In a prospective study of the effect of *CYP2B6* polymorphism on efavirenz concentrations and exposure, 456 patients infected with the human immunodeficiency virus type 1 (HIV-1) were genotyped for different SNPs, including the 499C>G, 15631G>T and 18053A>G polymorphisms [155]. All patients received the standard-dosage regimen of 600 mg/day, and extremely high concentrations (9,500 ± 2,580 ng/mL) were obtained in all 14 patients with the *CYP2B6*6/*6* genotype and in both patients with the *CYP2B6*6/*26* genotype. In contrast, only two patients with other *CYP2B6* genotypes had similarly high efavirenz concentrations, and both were heterozygous carrier of either the **6* allele (7,140 ng/mL) or **26* allele (9,710 ng/mL). Therefore, the **6* and **26* alleles were both associated with high efavirenz concentrations, and patients with the *CYP2B6*6/*6* or the *CYP2B6*6/*26* genotype had the highest concentrations with standard-dosage regimen of 600 mg/day.

To investigate the feasibility of dose reduction in patients with high efavirenz concentrations secondary to *CYP2B6* polymorphism, the investigators then reduced the efavirenz-dosage regimen to 400-mg/day in five patients and to 200 mg/day in another seven patients. The genotypes in these 12 patients included nine **6/*6* homozygotes, two **6/*26* heterozygotes, and one **1/*26* heterozygote. The plasma concentrations decreased proportionally with the dose reductions. Despite receiving the lower-dosage regimens for more than 6 months, the 12 patients were able to maintain therapeutically effective anti-HIV-1 activity with HIV-1 load continuously less than 50 copies/mL. Central nervous system side effects were reported to be much less frequent at the lower-dosage regimens. Similar therapeutic success with persistent suppressed HIV-1 load was also demonstrated in efavirenz-naïve patients (**6/*6* and **6/*26*), who were administered the lower-dosage regimen of 400-mg/day. The overall study results demonstrated the feasibility of genotype-based efavirenz-dose reduction in patients with *CYP2B6 *6/*6* and **6/*26* genotypes, with additional advantages of less central nervous system side effects and lower treatment cost.

CYP2A6

CYP2A6 only accounts for about 4% of total CYP450 content, and significant variations in CYP2A6 activity are primarily a result of genetic influence. The *CYP2A6* gene is located on chromosome 19 and codes for the protein CYP2A6 consisting of 494 amino acids. With more than 40 variants identified, the primary variants for *CYP2A6* polymorphism (www.cypalleles.ki.se) include *CYP2A6*2* (rs1801272, g.1799T >A), *CYP2A6*4* (gene deletion), *CYP2A6*5* (rs5031017 g.6582G > T), and *CYP2A6*20* (rs28399444, frame shift), all of which are associated with abolished enzyme activity. Additional alleles associated with reduced enzyme activity include *7 (rs5031016, g.6558 T>C), *10 (rs28399468, g.6600G>T) *11 (rs111033610. g.3391T>C), *17 (rs28399454, g.5065G>A), *18 (rs1809810 g.5668A>T), and *19 (rs5031016 g.6558T>C). As with other CYP polymorphisms, there are substantial interethnic differences in allele frequency. Deletion of the *CYP2A6* gene is very common in Asian patients [166], which likely accounts for the dramatic difference in the high occurrence of PMs in Asian (20%) versus Caucasian populations (≤1%).

Nicotine is metabolized by CYP2A6 to cotinine, and the clinical relevance of the *CYP2A6* polymorphism has been primarily investigated in managing patients with tobacco abuse. Nonsmokers were found to be more likely to carry defective *CYP2A6* alleles such as *7 and *9 than were smokers. In addition, smokers with defective *CYP2A6* alleles smoked fewer cigarettes and were more likely to quit. These results likely reflect higher nicotine concentrations, enhanced nicotine tolerance and increased adverse effects from nicotine in CYP2A6 poor metabolizers. Based on these observations, CYP2A6 inhibition may have a role in the management of tobacco dependency [166].

CYP1A2

Located on chromosome 15, *CYP1A2* consists of 7,758 nucleotides and encodes the enzyme CYP1A2 that contains 516 amino acids. Polymorphisms of the CYP1 family of genes have been studied for association with cancer susceptibility. Several *CYP1A2* SNPs have been identified, including *CYP1A2*1C* (rs2069514, –3860G>A) and the haplotype *CYP1A2*1K* containing three variants: –739T>G (rs2069526), –729C>T (rs12720461), and –163C>A (rs762551). However, to date there has been no consistent report of any functional *CYP1A2* alleles that result in important changes in gene expression and enzyme activity. Therefore, in contrast to other CYP isoenzymes such as CYP2C19 and CYP2C9, there is less agreement in the literature regarding acceptable method of defining CYP1A2 metabolic phenotype by *CYP1A2* genotype.

Nevertheless, a unique aspect of the *CYP1A2* gene is that a specific allele, *CYP1A2*1F* (rs762551) containing a c.-163C>A mutation in intron 1, has been shown to affect CYP1A2 inducibility [167] and the magnitude of increased caffeine metabolism in smokers [168,169]. However, conflicting reports have been reported for other CYP1A2 substrates [170–172]. This gene–environment interaction makes genotype–phenotype prediction of phenotype much more difficult. Finally, promoter variation is less likely to result in substrate-dependent effects, and the functional importance of increased CYP1A2 inducibility is currently unknown.

CYP1A2 contributes up to 10% of the total hepatic P450 content. However, unlike other CYP isoenzymes, it only mediates the metabolism of several commonly used drugs such as olanzapine, clozapine, duloxetine, and theophylline [173,174]. Although pharmacokinetic studies evaluating CYP1A2 inducibility by smoking or omeprazole have been performed, none of the studies have produced consensus information.

POLYMORPHISMS IN NON-CYP450 DRUG-METABOLIZING ENZYMES

Genetic polymorphisms in many non-P450 enzymes also play a role in influencing metabolism and elimination of many drugs. Among these enzymes, UDP-glucuronosyl transferase (UGT), thiopurine-*S*-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), *N*-acetyltransferase (NAT), and glutathione-s-transferase (GST) have been characterized and their clinical relevance studied.

UDP-Glucuronosyl Transferase

The uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes are divided into two distinct subfamilies: UGT1 and UGT2. UGT1A1 has been the most extensively investigated among the UGT1A enzymes. A polymorphism with an extra thymine-adenine (TA) repeat (TA insertion) in the 5′-promoter region of the *UGT1A1* gene results in the *(TA)^{7}TAA* allele or *UGT1A1*28* (rs8175347), with a 35% decrease in transcriptional activity of *UGT1A1* and lower enzyme activity than the wild-type *(TA)^{6}TAA* allele (*UGT1A1*1*) [175]. Another UGT1A1 polymorphism, *UGT1A1*6* (rs4148323) carrying the c.211G>A SNP and p.G71R substitution in exon 1, has also been associated with lower enzymatic activity [176]. Although the **28* variant is more common in Caucasians (29%–40%) and Africans (36%–43%) than in Asians (13%–16%), the **6* is found only in Asians with a frequency of 16%–23%.

UGT contributes about 35% of phase II drug metabolism and is involved in glucuronidation of endogenous compounds and xenobiotics. For UGT1A1, the substrates include bilirubin, SN-38 (active and toxic metabolite of the anticancer drug irinotecan), raltegravir (inhibitor of the HIV integrase enzyme), clozapine, bazedoxifene (an investigational selective estrogen receptor modulator for prevention and treatment of postmenopausal osteoporosis), and eltrombopag (a thrombopoietin receptor agonist for the management of thrombocytopenia).

Irinotecan, also known as CPT-11, is a prodrug that requires metabolic activation via carboxylesterase to SN-38, a potent inhibitor of topoisomerase I. SN-38 is inactivated via glucuronidation by the polymorphic *UGT1A1* enzyme. Both *UGT1A1*28* and **6* had been associated with impaired SN-38 glucuronidation, especially in patients who are homozygous carriers (*UGT1A1*28 TA7/TA7*) [176,177]. The ensuing high SN-38 concentrations lead to increased SN-38 excretion into the gut lumen, predisposing patients to severe diarrhea even with standard irinotecan-dosage regimens. Abnormally high SN-38 concentrations have also been reported in patients with severe neutropenia [178]. These pharmacogenetic-related adverse reactions have also been demonstrated in prospective clinical trial [179] that led to FDA approval of the Invader UGT1A1 Molecular Assay (Third Wave Technologies) for genotyping *UGT1A1* alleles and revision of the irinotecan product label to include consideration of lower initial dose requirement for individuals who are homozygous for *UGT1A1*28*, although the genetic testing is not a requirement. The predictive value of *UGT1A1*28* polymorphism has recently been confirmed in a meta-analysis of 58 studies [180]. With the involvement of UGT1A1 in bilirubin glucuronidation confirmed by three meta-analyses [181–183] and the prevalence of *UGT1A1*6* among Asian populations, UGT1A1 may play a role in the high incidence of neonatal hyperbilirubinemia in those populations [184].

A different UGT enzyme, UGT2B7, plays an important role in mediating the conversion of morphine to the pharmacologically active metabolite, morphine-6-glucuronide. Darbari et al. reported that homozygous and heterozygous carriers of the G variant for the -840 G>A SNP (rs7438135) had significant higher parent to metabolite concentration ratio compared to individuals with the *A/A* genotype ($P = .03$) [185]. A second *UGT2B7* SNP (rs7439366, C802T) was

implicated for morphine toxicity in a patient with the *T/T* genotype that resulted in increased morphine-6-glucuronide formation [186].

Thiopurine-*S*-methyltransferase

Thiopurine-S-methyltransferase (TPMT) is encoded by the *TPMT* gene that has a nonsynonymous SNP and resulting in reduced TPMT enzymatic activity. Although more than 31 variants of the *TPMT* gene have been identified, the five most studied one are *TPMT**2 (rs1800462, G238>C, reduced activity), *TPMT*3A* (a haplotype consisting of the two nonsynonymous SNPs, G460>A and A719>G, abolished activity), *TPMT*3B* (rs1800460, G460>A, reduced activity) *TPMT*3C* (rs1142345, A719>G, reduced activity), and *TPMT*4* (rs1800584, G626>A, very low activity). About 95% of intermediate or low TPMT activity in affected patients are associated with *TPMT**2, *TPMT*3A*, or *TPMT*3C*. Approximately 10% and 0.3% of the Caucasian population is heterozygous and homozygous, respectively, of these mutant alleles.

TPMT mediates the inactivation of thiopurine drugs, including thioguanine, 6-mercaptopurine, and its precursor, azathioprine. Compared to patients who possess the wild-type alleles, homozygotes or heterozygotes for the *TPMT* mutant alleles have much higher levels of the cytotoxic thiopurine nucleotides and are at higher risk for developing serious hematological toxicities during treatment with standard-dosage regimens of the thiopurine drugs [187]. As a result, patients with absent and low TPMT activity can only tolerate 5 and 50% of the standard 6-mercaptopurine regimen.

The TPMT metabolism represents one of the most-investigated drug metabolic pathways that demonstrates the clinical relevance of genetic polymorphism. Currently, TPMT is the only drug-metabolizing enzyme with significant acceptance and widespread testing in clinical practice, with genotyping or phenotyping (determination of TPMT activity in red blood cells) recommended by the FDA, and the thiopurine drugs are one of several medications that have clinical guidelines available through the CPIC [188,189].

Dihydropyrimidine Dehydrogenase (DYPD)

In addition to being the initial and rate-limiting enzyme that catalyzes pyrimidines such as uracil and thymine, dihydropyrimidine dehydrogenase (DYPD), a minor phase I metabolizing enzyme, also mediates the metabolism of 5-fluorouracil (5-FU) and capecitabine. Genetic polymorphisms in the *DPYD* gene that encodes DYPD result in DYPD-deficiency phenotypes with an overall frequency in the general population of about 3%–5%, which varies significantly among many ethnic groups [190].

With more than 30 SNPs in *DYPD*, the most-relevant decreased functional variants associated with grade 3- and grade 4-toxicities in 5-FU-treated patients include c.1905+1G>A, also known in the literature as *DYPD*2A* or *DYPD*:IVS14+1G>A (rs3918290); c.1679 T>G, also known as *DYPD*13* (rs55886062, p.I560S); c.2846A>T (rs67376798 p.D949V); and c.1129-5923C>G (rs75017182) [191,192]. Other variants such as c.85T>C (*DYPD*9A*, rs1801265, p.C29R) do not result in altered DYPD activity [193]. Among the four functional SNPs, the G>A mutation within intron 14 results in a protein with no catalytic activity and is found in approximately 40%–50% of patients who have either a partial or complete DYPD deficiency. Homozygous and heterozygous carriers of the variant IVS14+1G>A allele have complete absence and 50%, respectively, of normal DYPD activity, and significant, sometimes life-threatening 5-FU-related toxicities [194]. However, the risk of severe toxicity is not necessarily related to *DYPD* genotypes [195]. This may be due to sensitivity of the *DYPD* genetic testing being dependent on which *DYPD* variants are included in specific test panels [193].

N-acetyltransferase

Genetic polymorphism in acetylation capacity was reported more than 50 yrs ago, when two distinct phenotypes of rapid acetylator (RA) and slow acetylator (SA) were noted in patients enrolled in a clinical trial of the antituberculosis drug isoniazid [196]. Subsequently, the phenotype differences were associated with enzyme activities of two cytosolic enzymes N-acetyltransferase-1 (NAT1) and N-acetyltransferase-2 (NAT2), which are encoded by the *NAT1* and *NAT2* genes, respectively. The NAT2 enzyme is primarily responsible for acetylation of aromatic amines and hydrazines. Polymorphism in *NAT2* results in more than 10 *NAT2* alleles, with *NAT2*4* reported as the wild-type allele, and *NAT2*5* (rs1801280) carrying the c.341T>C SNP that results in the p.I114T amino acid change, *NAT2*6* (rs1799930) with c.590G>A SNP and p.R197Q substitution, as well as NAT2*7 (rs1799931) with c.857G>A SNP and corresponding p.G286E substitution as the primary variant alleles [197]. These three variant alleles account for the majority of the SA phenotype. The prevalence of SAs varies significantly in different ethnic groups: 90% of Arab populations, 40%–60% of Caucasians, and 5%–25% of East Asians.

Substrates for NAT include numerous arylamine- and hydrazine-containing drugs such as sulfamethoxazole, hydralazine, isoniazid, and procainamide. High blood levels of these and similarly, acetylated drugs in SAs have been associated with lupus-like syndrome (hydralazine and procainamide), peripheral neuropathy (isoniazid), and liver damage (sulfapyridine). In addition, to drug therapy, *NAT2* polymorphism has also been implicated in susceptibility to developing different types of cancer, with SA having an increased risk after prolonged exposure to carcinogenic arylamines and other industrial chemicals [198].

Glutathione-S-transferase

The human glutathione-S-transferase (GST) family of cytosolic enzymes contains at least 17 genes divided into seven classes:α, μ, π, σ, θ, ζ, and ω. Of these, the most important genes are *GSTM1* of the μ class, *GSTT1* of the θ class, *GSTP1* of the π class, and *GSTA1* of the α class. Both deletion polymorphisms and SNPs exist for *GST* genes. Gene deletion results in the null variants, *GSTM1*0* and *GSTT1*0* and loss of GSTM1 and GSTT1 enzyme function, respectively. Two polymorphisms of the *GSTP1* gene have been described: rs947894 carrying the exon 5 c.A1404G SNP, and p.I105V substitution at codon 105, and rs1799811 carrying the exon 6 c.C2294T SNP and p.A114V substitution at codon 114. Four different haplotypes have been described for the population: *GSTP1*A* (^{105}Ile-^{114}Ala), *GSTP1*B* (^{105}Val-^{114}Ala), *GSTP1*C* (^{105}Val-^{114}Val), and *GSTP1*D* (^{105}ILe-^{114}Val) [199]. A point mutation in the promoter of the *GSTA1* gene results in lower promoter activity associated with the *GSTA1*B* allele. In contrast to deleted *GST* genotypes, the *GSTP1* and *GSTA1* polymorphisms result in genotypes with low-activity enzymes.

The frequency of occurrence of the two *GST* null alleles varies significantly among different populations. Between 42% and 58% of Caucasians and 27%–41% of Africans are reported to be lacking the *GSTM1* gene. For the *GSTT1* gene, the null-allele frequency ranges from 2% to 42% for Caucasians, 50%–60% in Asians, 15%–20% of African Americans, and less than 10% in Hispanics [200,201]. The *GSTP1* and *GSTA1* polymorphisms have been reported to occur in up to 40% of Caucasians and 54% of Africans, and 40% of Caucasians and 41% of Africans, respectively.

GSTs are detoxification enzymes that mediate the conjugation of reduced glutathione with different substrates that include carcinogens and chemotherapeutic agents, such as oxaliplatin-based chemotherapy and chlorambucil

[200,202–204], with poorer response and reduced overall survival in patients with *GSTM1*0* or *GSTT1*0* genotypes, and treated with oxaliplatin-based chemotherapy or anthracycline-based induction therapy [204–207]. Because GSTs are detoxification enzymes, the shortened survival in patients with reduced GST activity might be related to severe drug-related toxicity, as evidenced by a higher frequency of grade 4 neutropenia in homozygous carriers of *GSTM1*0* and treated with oxaliplatin-based chemotherapy for their metastatic colorectal cancer [208]. The important detoxification role of GST has also been reported in a recent study in which pediatric patients with *GSTMI* and *CYP2C9* variants have a higher risk of developing hemorrhagic cystitis when treated with the combined regimen of busulfan and cyclophosphamide [209].

POLYMORPHISMS IN DRUG-TRANSPORTER GENES

Membrane transporters are present at many endothelial and epithelial barriers, including the blood brain barrier (BBB), the intestinal epithelial cells, the hepatocytes, and the renal tubular cells. By facilitating drug excretion into the gastrointestinal tract and bile, from the liver and kidney, as well as limiting the amount of drug crossing the BBB, they provide an important physiological role of protecting humans against toxic xenobiotics, and have recently been recognized as important determinants of drug disposition and response [210]. These drug transporters can be broadly classified into two groups: the efflux adenosine triphosphate-binding cassette (ABC, and formerly known as multidrug resistance [MDR]) family of transporters, and the uptake solute carrier (SLC) family of transporters. In all, 49 members are present within the human ABC-transporter family. Based on homology of their amino acid sequences, they are further classified into seven subfamilies. Of all the ABC transporters, the better-known examples are ABCB1 (P-glycoprotein [Pgp] or MDR1), ABCC1 (multidrug resistance 1 [MRP1]), ABBC2 (multidrug resistance [MRP2]), and ABCG2 (breast cancer resistance protein [BCRP]). For the SLC family, there are 360 members that are subdivided into 46 subfamilies. The better-known SLC transporters are organic anion-transporting polypeptide (OATP), organic cation transporter (OCT), and organic anion transporter (OAT). Genetic variants of the genes encoding these drug-transport proteins (http://www.pharmGKB.org) have been discovered that affect their expression, substrate specificity, and/or intrinsic transport activity, and ultimately disposition, efficacy, and safety of many drug substrates.

The ABC-Efflux Transporters

ABCB1

ABCB1 was the first recognized and the most-studied ABC transporter. It is encoded by the highly polymorphic *ABCB1*, with more than 50 SNPs and three insertion/deletion polymorphisms reported. The most common studied SNPs are the c.C1236T (rs1128503) silent polymorphism in exon 12, the c.G2677A/T (rs2032582) polymorphism in exon 21, and the c.C3435T (rs1045642) silent polymorphism in exon 26. The c.G2677A/T polymorphism results in a change in amino acid sequence p.A893S (G2677T) SNP or p. A893T (G2677A) SNP. Ethnic variations in allelic variant distribution are well known [211,212]. In addition, strong LD among these SNPs had been reported to create haplotypes consisting of 1236C>T, 2677G>A/T, and 3435C>T. The three *ABCB1* SNPs and their haplotypes (Table 1.3) are important in expression and function of ABCB1.

The functional and clinical implication of the *ABCB1* polymorphism was first evaluated for the C3435T SNP with digoxin as the substrate, demonstrating a relationship between lower

TABLE 1.3 Selected ABC Transporters Polymorphisms Indicating Allele Variants and Frequency, and Drug Substrates

Genes	Allele Variants, Amino Acid Change	Frequency (%)	Drug Substrate Examples
ABCB1	C3435T	48%–59% in Caucasians 37%–66% in Asians 10%–27% in Africans	Protease inhibitors (ritonavir, saquinavir, nelfinavir) Anticancer drugs (anthracyclines, taxanes, vinca alkaloids, imatinib) Immunosuppressants (cyclosporine, tacrolimus) Antibiotics (erythromycin, levofloxacin) Calcium channel blockers (diltiazem, verapamil) Digoxin, pivastatin, simvastatin
	C1236T	34%–42% in Caucasians 60%–72% in Asians 15%–21% in Africans	
	G2677T, A893S	38%–47% in Caucasians 32%–62% in Asians ≤15% in Africans	
	G2677A, A893T	1%–10% in Caucasians 3%–22% in Asians	
	1236C>T/2677G>T/3435C>T haplotype	23%–42% in Caucasians 28%–56% in Asians 4.5%–8.7% in Africans	
ABCC2	1249G>A, V417I	22%–26% in Caucasians 13%–19% in Asians 14% in Africans	Reverse transcriptase inhibitors (tenofovir), Anticancer drugs (anthracyclines, vinca alkaloids, methotrexate, SN-38 glucuronide), pravastatin, rifampin
ABCG2	421C>A, Q141K	6%–14% in Caucasians 15%–36% in Asians 0%–5% in Africans	Anticancer drugs (methotrexate, imatinib, gefitinib, SN-38, SN-38 glucuronide, topotecan), Apixaban, atorvastatin, rosuvastatin, glyburide, dolutegravir

expression of ABCB1 and increased digoxin bioavailability and plasma concentration after oral administration in TT homozygotes with reduced ABCB1 activity [213]. In two separate studies, investigators showed that CC genotype of the C3435T SNP (increased Pgp expression) is associated with reduced efficacy and a higher risk of myalgia after treatment with atorvastatin [214] and increased statin-associated increase in serum creatine kinase [215], presumably due to lower intracellular concentration and higher plasma concentration of statin.

The polymorphism also affects plasma concentrations and clinical effects of protease inhibitors. After 6-mo therapy with efavirenz or nelfinavir, patients with the TT genotype had a greater rise in cluster of differentiation 4 (CD4) cell counts than patients with the CC genotype [216]. Therefore, *ABCB1* genotyping may have a role in predicting responses to protease inhibitors. The *ABCB1* haplotype TTT (rs1128503, rs2032582, rs1045642) was reported to be responsible for increased morphine exposure and the exhibition of morphine sensitivity in a patient [186]. In addition, Sadhasivam et al. reported an association between another *ABCB1* variant (rs9282564) and increased risk of morphine-induced respiratory depression in patients with the GG and GA genotypes of this SNP [217].

Nevertheless, conflicting results have been reported regarding the functional and clinical significance of the polymorphism for different substrates including psychotropics (see Chapter 7), antiretroviral protease inhibitors, immunosuppressants, and anticancer drugs. This may be due to the use of different assays

and study designs to identify ABCB1 substrates, the overlapping substrate specificity between ABCB1 and other enzymes and transporters; e.g., CYP3A4 for cyclosporine and OATP transporters for fexofenadine [218], the existence of strong LD necessitating a haplotype approach rather than individual SNPs in association studies or clinical evaluations. In addition, the 1236C>T/2677G>T/3435C>T haplotype was shown to affect the inhibition of substrate transport and not the transport process per se [219]. Thus, the functional effect of *ABCB1* polymorphism may be more modest than previously thought. Whether additional mutations resulting in loss of function, significant change in substrate specificity or functionality would have a bigger impact is not known, and awaits further studies for clarification [219,220].

ABCC1 and ABCC2

Both ABCC1 and ABCC2 are involved in the biliary excretion of conjugated drugs such as glucuronides or sulfates of tamoxifen and SN-38 glucuronide [221,222], organic anions, and some nonconjugated drugs such as methotrexate and pravastatin (Table 1.3), and exhibit overlapping substrate specificities for a variety of drugs. Genetic variation in *ABCC1* gene is rare, whereas polymorphisms of *ABCC2* gene are more common, including the c.1249G>A SNP (rs2273697) in exon 10 resulting in a p.V417I substitution and lower protein expression. Another identified polymorphism is the c.3972C>T SNP (rs3740066) in exon 28 with a p.I324I amino acid substitution [223].

Patients with the 1249G>A variant and receiving tenofovir were reported to have higher risk of drug-induced renal proximal tubulopathy, possibly a result of reduced renal drug excretion [224]. In an exploratory study of an association between *ABCC2* polymorphisms and haplotypes with irinotecan disposition in a cohort of 167 Caucasian patients with solid tumors, a total of 15 *ABCC2* haplotypes were constructed from six variants of *ABCC2* gene. The *ABCC2*2* haplotype (low activity) was found to be associated with lower irinotecan clearance of 28.3 L/h in 48 patients compared with 31.6 L/h in 75 patients not carrying the haplotype ($P = .02$). Interestingly, patients carrying the *ABCC2*2* haplotype but not the *UGT1A1*28* allele experienced lower incidence of severe grade 3–4 diarrhea (odds ratio of 0.15) compared to patients carrying at least one *UGT1A1*28* allele (odds ratio of 1.87), suggesting a protective effect of *ABCC2*2* haplotype against diarrhea occurrence [225]. Because ABCC2 mediates the secretion of SN-38 glucuronide into the bile, the protective effect might reflect a lower exposure of intestinal epithelial cells to SN-38 that is formed after cleavage of SN-38 glucuronide by β-glucuronidase within the intestine (Fig. 1.2).

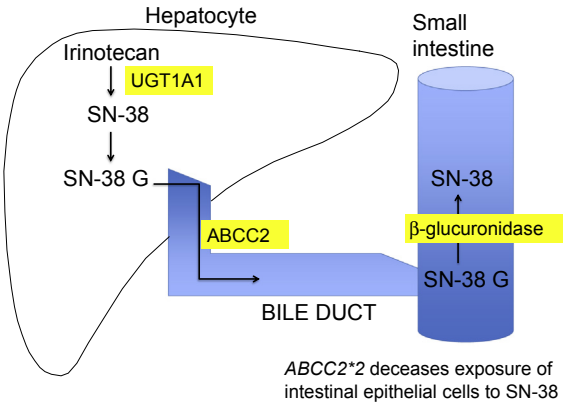

FIGURE 1.2 Schematic representation of potential protective effect of ABCC2 polymorphism against irinotecan-induced diarrhea.

ABCG2

The *ABCG2* gene encodes the BCRP, which is also known as mitoxantrone resistant protein (MXR), or placenta-specific ATP binding cassette transporter (ABCP). More than 80 polymorphisms in *ABCG2* have been reported, with the most studied being the c.421C>A SNP (rs2231142, p.Gln141Lys) in exon 5 that results in a p.Q141K substitution and lower protein expression (Table 1.3) [226]. The c.421C>A

variant with K141 is commonly present in different ethnic groups, being more common in Asians and Caucasians than in sub-Saharan Africans [211,212,227].

Patients carrying the c.421C>A SNP were reported to have increased concentrations of gefitinib and topotecan [228,229], resulting in higher incidence of gefitinib-induced diarrhea [230]. Increased risk of diarrhea was also associated with the *ABCG2* polymorphism in patients with cancer and receiving rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (R–CHOP) therapy [231]. ABCG2 also plays a role in disposition of other drugs, with the c.421C>A variant reducing biliary excretion of apixaban [232], dolutegravir [233], and rosuvastatin [234]. In 305 Chinese patients with hypercholesterolemia treated with 10 mg of rosuvastatin per day, a gene dose-dependent reduction in low-density lipoprotein cholesterol levels was observed in a carrier of the C421A variant [235]. In both the JUPITER trial, with more than 4,000 patients, and another study with a cohort of 291 Chinese patients, a strong association at the genome-wide level significance has been reported between the C421A variant and altered statin efficacy [236,237].

The SLC-Uptake Transporters

Organic Anion Transporting Polypeptides

In contrast to ABCB1, OATPs are influx or uptake transporters. In addition, to facilitating hepatic uptake of drugs such as statins and antidiabetic agents from the blood into hepatocytes for further metabolism or biliary secretion, OATP also mediates the transport of several endogenous compounds, including bile salts, across the cell membrane. A total of 11 OATP transporters have been identified and classified into six families [238]. Of the human OATPs, OATP1A2, OATP1B1, OATP1B3, and OATP2B1 (Table 1.4) are the best characterized.

OAT1B1

The human *SLCO1B1* gene encodes OATP1B1, which is also known as OATP-C. Since the discovery of the first c.521T>C SNP [239], multiple SNPs have been reported for *SLCO1B1*, with 17 different *SLCO1B1* alleles identified [240]. The 521T>C SNP (rs4149056) with p.V174A substitution results in lower expression of the OATP1B1 protein and reduced transport activity. The 521T>C SNP is more common in Caucasians and Asians than in Africans (Table 1.4). Another very common mutation in all investigated ethnic groups is the c.388A>G SNP (rs2306283) resulting in p.N130D substitution, although conflicting results exist regarding associated changes in transport activity. More importantly, though, the 521T>C SNP and 388A>G SNP are in LD, resulting in several functionally distinct haplotypes, e.g., *OATB1B1*5* carrying the 388A/521C, *OATB1B1*15* carrying the 388G/521C, and *OATB1B1*17* carrying the 388G/521C with -11187A/-10499A of two additional SNPs in the promoter region of *SLCO1B1* [240,241]. Both **5* and **15* haplotypes contain the 521C allele and have been associated with reduced activity.

OATP1B1 plays an important role in hepatic uptake of the 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors such as pravastatin and rosuvastatin, as well as simvastatin acid, the active metabolite of simvastatin. The 521T>C variant has been associated with altered pharmacokinetics of simvastatin acid, with the CC homozygotes having more than two–three-fold increased systemic exposure compared to the other two genotypes [242], potentially resulting in increased toxicity [243], and with decreased intracellular concentration of simvastatin acid for inhibiting HMG-CoA reductase in hepatocytes, a lower efficacy for cholesterol reduction [244]. In a GWAS, 316,184 SNPs were compared between 96 patients treated with 80 mg/day of simvastatin and suffering from myopathy and 96 control subjects without the adverse drug effect. A noncoding rs4363657

TABLE 1.4 Selected SLC Transporters Polymorphisms Indicating Allele Variants and Frequency, and Drug Substrates

Genes	Allele Variants, Amino Acid Change	Frequency (%)	Drug Substrate Examples
SLCO1B1	521T>C, V174A	8%–22% in Caucasians 1%–19% in Asians 1%–5% in Africans	HMG-CoA reductase inhibitors (atorvastatin, simvastatin acid, pravastatin, rosuvasatatin), Anticancer drugs (SN-38, methotrexate), Antibacterials (rifampicin, cefazolin), repaglinide, valsartan
	388A>G, N130D	30%–46% in Caucasians 54%–84% in Asians 72%–81% in Africans	
SLCO2B1	1457C>T, S486F	1%–6% in Caucasians 25%–36% in Asians 10%–41% in Africans	HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, pravastatin, rosuvasatatin), glibenclamide, fexofenadine, motelukast
	935G>A, R312Q	2%–14% in Caucasians 21%–40% in Asians 7%–15% in Africans	
SLCO1B3	334T>G, S112A	74%–89% in Caucasians 64%–83% in Asians 35%–41% in Africans	Anticancer drugs (docetaxel, paclitaxel), digoxin
	699G>A, M233I	71%–90% in Caucasians 64%–84% in Asians 34%–48% in Africans	
SLC22A1	1201G>A, G401S	1% in Caucasians 0% in Asians 1% in Africans	Metformin
	1393G>A, G465R	4% in Caucasians 0% in Asians, Africans	
	1256delATG, M420del	60% in Caucasians 74%–81% in Asians 74% in Africans	
SLC22A2	808G>T, A270S	16% in Caucasians 14%–17% in Asians 11% in Africans	Metformin

SNP within intron 11 of *SLCO1B1*, found to be in nearly complete LD with the rs4149056 polymorphism (521T>C, V174A) ($r^2 > 0.95$), was identified as the only strong SNP marker associated with simvastatin-induced myopathy. The odds ratio (OR) for myopathy was reported as 4.3 per copy of the C allele, and 17.4 in CC homozygotes compared with TT homozygotes [245].

In a more recent study, carriers of the T521C SNP were shown to have an OR of 8.86 ($P < .01$) for statin-induced serum creatine kinase elevation, whereas the impact of the A388G SNP was much smaller (OR of 0.24, $P < .05$) [215]. The magnitude of the clinical significance shown in these two studies [215,245] suggests potential value of genotyping to screen out patients with abnormal OATP1B1 activity to improve the therapeutic index of simvastatin, and may be for other HMG-CoA reductase inhibitors such as pravastatin that are also OATP1B1 substrates [246–248]. Indeed, both the 521T>C SNP and *SLCO1B1*17* haplotype had been shown to be associated with increased

pravastatin concentrations and decreased efficacy [249–251]. Based on the results of these and other studies, the CPIC has made recommendations for genotype-based dosing of statins in its 2014 guideline update [252]. In addition, both SLCO1B1 drug–drug interaction with concurrent drug therapy and drug–gene interaction with *SLCO1B1* variants can alter statin transport and subsequent metabolism and, hence, the risk for statin-related ADR such as rhabdomyolysis [253].

OATP2B1

OATP2B1, also known as OATP-B, possesses substrate selectivity similar to that of OATP1B1 [254]. OATP2B1 has also been found to be expressed in the luminal membrane of the small intestinal enterocytes [255], and hence would have a role in drug absorption. Since the first discovery of genetic polymorphism, several sequence mutations of *OATP2B1* have been described, including the c.1457C>T SNP (rs2306168), c.601G>A SNP (rs35199625), c.935G>A SNP (rs12422149), c.43C>T SNP (rs56837383), and a nine-nucleotide deletion of three amino acids 26–28 (26–28, p.QNT) of *OATP2B1* [256]. Although decreased transport activity had been shown mostly in vitro for most of these SNPs, the results are not consistent among all studies. In addition, significant ethnic variabilities exist in allele frequency of these SNPs; for example, the allelic frequency of c.1457C>T SNP is higher in Asians (31%) compared to Caucasians (3%)

A recent study evaluated the impact of the 1457C>T SNP on fexofenadine pharmacokinetics in Japanese subjects, and found similar pharmacokinetic parameters among the three genotype groups [257]. Although the same SNP did not affect the absorption of the leukotriene receptor antagonist motelukast, patients who carry the 935A variant allele of the c.935G>A SNP was reported to show lower plasma concentration and lesser pharmacological response [258]. Yet a separate study reported the lack of an association between motelukast and the c.935G>A SNP. Although this might suggest that the effect of *SLCO2B1* SNP on drug absorption could be substrate dependent, more importantly, additional studies with other substrates would need to be performed for clarification of the effect of *SLCO2B1* on drug disposition.

OATP1B3

In humans, the *SLCO1B3* gene encodes OATP1B3, which was previously also known as OATP8 and LST-2. Several sequence variations exist for the *SLCO1B3* gene. The c.334T>G SNP (rs4149117) and the c.699G>A SNP (rs7311358) occur at a high frequency in Caucasian populations. Although OATP1B3 mediates the hepatic uptake of several drugs, including taxanes [259], a study in 90 patients with cancer from six different ethnic groups reported that there were no associations between paclitaxel clearance and the two *OATP1B3* SNPs [260]. Similarly, no associations were found between docetaxel pharmacokinetics and OATP1B3 SNPs [261,262]. The role of *OATP1B3* polymorphisms in drug disposition and response await further clarification from future studies.

In summary, OATP polymorphisms can affect disposition and possibly response for a large number of drugs. Current evidence strongly suggests a vital role of specific SNPs of *SLCO1B1* gene (e.g., 521T>C) for statin efficacy and adverse effects. Similar data for other OATP1B1 substrates from future clinical studies would provide further evidence of the value of prospective genotyping for *SLCO1B1* variants in individualizing drug therapy. In contrast, the data for validating the functional role of *SLCO2B1* and *SLCO1B3* polymorphisms are not as clear. Much more work is needed for clarifying the clinical significance of these SNPs for predicting pharmacokinetic profile for, and clinical response to, OATP2B1 and OATP1B3 substrates.

Organic Cation Transporters

Three organic cation transporters (OCTs) have been identified in humans: OCT1, OCT2,

and OCT3, all of which are members of the SLC22A family, and are encoded by the corresponding *SLC22A1*, *SLC22A2*, and *SLC22A3* genes, respectively (Table 1.4). OCT1 is primarily expressed in the hepatocytes and mediates cellular uptake of drugs into the liver. OCT2 is primarily expressed in the proximal tubules of the kidney. In contrast, OCT3 is more broadly distributed in the body.

Located on chromosome 6, *SLC22A1* is highly polymorphic with reduced or loss of transporter functional activity secondary to four coding polymorphisms: c.181C>T (rs12208357, p.Arg61Cys), c.1393G>A (rs34059508, p.Gly465Arg), c.1201G>A (rs34130495, p.Gly401Ser), and OCT1 Met420 deletion of three bases ATG at codon 420 of exon 7 and collectively designated as rs72552763 [263]. The Met420 deletion variant commonly occurs in Caucasians and African Americans with a frequency of 18.5% and 5%, respectively. OCT1 genotypes have been shown to contribute to interindividual variability in disposition of several drugs, including ondansetron, metformin, morphine, and tramadol [264–267].

Of the different SNPs that have been identified for the *SLC22A2* gene, the most relevant one is the c.808G>T SNP (rs316019) that results in the p.A270S substitution. The antidiabetic drug metformin is primarily renally eliminated by active tubular secretion via OCT2. Homozygotes of the low-activity 270S variant had been shown to have lower renal clearance and higher plasma concentrations of metformin when compared to homozygous carriers of the wild-type 270A [268,269]. Interestingly, Tzvetkov et al. demonstrated that OCT1 is also expressed in the distal tubule and may play a role in tubular reabsorption of metformin. They reported that homozygous and heterozygous carriers of various haplotypes of low-activity alleles of several *SLC22A1* polymorphisms (c.1201G>A SNP with p.G401S substitution, c.1393G>A SNP with p.G465R substitution, and a deletion resulting in M420del) were associated with increases in metformin renal clearance by about 20%–30% [267]. Nevertheless, OCT1 is primarily expressed in the hepatocyte, the major site of action of metformin. The same low-activity OCT1 variant alleles of these polymorphisms have also been reported to decrease hepatic uptake of metformin with resultant lower blood glucose response [270], and more recently for fenoterol, resulting in increased systemic exposure and drug-related toxicities [271]. The effects of genetic polymorphisms in other transporters such as the multidrug and toxin extrusion transporters as well as pharmacological targets for metformin is further discussed in Chapter 9.

Organic Anion Transporters

In contrast to the OCT belonging to the same SLC22 family, the organic anion transporters (OATs) primarily mediates the transport of organic anions. Four OATs have been studied regarding their tissue location: OAT1, OAT2, and OAT3 are primarily expressed in the basolateral membrane of the renal proximal tubule, whereas OAT4 is located at the apical side. Therefore, OAT1, OAT2, and OAT3 are responsible for uptake of drug substrates into the tubular cells and OAT4 mediates their secretion into the renal tubule. Although several polymorphisms have been reported for *SLC22A6* encoding OAT1, SLC22A7 encoding OAT2, *SLC22A8* encoding OAT3, and *SLC22A11* encoding OAT4, the allele frequency of these SNPs are all ≤1% and their functional significance have not been clarified [272,273].

POLYMORPHISMS IN DRUG-TARGET GENES

The study of pharmacodynamics encompasses the biochemical and physiological effects of drugs on the body and the relationship between drug concentration and drug effect. Drugs exert their effects through interaction with numerous protein types, including cell

surface receptors (e.g., β-adrenergic, 5-hydroxytryptamine receptors, and μ–opioid receptors), enzymes (e.g., vitamin K epoxide reductase complex 1, adenosine monophosphate-activated protein kinase, and catecho-O-methyltransferase), and ion channel proteins (e.g., sodium and potassium channels, epithelial sodium channel). Additionally, numerous intracellular signaling proteins downstream from the target protein are involved in eliciting drug response. Genetic variation affecting either the activity or expression of a drug-target or intracellular signaling protein can have significant consequences for pharmacodynamic drug response.

Phenotypic response to genetic variation for drug-target proteins generally differs from that of drug-metabolizing enzymes and drug transporters (Table 1.5). As illustrated in Fig. 1.3, variation in drug-metabolizing enzymes results in distinct phenotypes (e.g., PMs, EMs, or UMs), as described in the earlier section. With precision oncology the expression of drug-target receptor gene for tumor cells predicts drug efficacy. In addition, there are a limited number of examples of genetic variants in drug-target proteins in germline cells that result in distinct pharmacodynamic effects. One of these examples involves mutations in the vitamin K epoxide complex subunit 1 *(VKORC1)* gene, in which rare nonsynonymous mutations result in warfarin resistance, and exceptional high doses (30 mg/day or higher) are required to achieve therapeutic anticoagulation. Most polymorphisms that impact drug pharmacodynamics tend to be much more subtle and help explain response variability across a single distribution curve. For example, commonly occurring variations in the *VKORC1* regulatory regions help explain the significant interpatient variability in the warfarin dose required to produce optimal anticoagulation, as described in detail in Chapter 6. The remainder of this section discusses examples of genes for various types of drug-target proteins that contribute to the interpatient variability in pharmacodynamic drug responses.

Drug Target Receptor Genes in Oncology

Several cancer chemotherapy agents have been developed based on findings that overexpression of certain tumor cell surface receptors drives tumor cell growth and which are further described in Chapters 3 and 5. Expression of the epidermal growth factor receptor type 2 (HER2), also known as Her2/neu and ErbB2, is one such example that influences disease prognosis and predicts drug. Overexpression of HER2 occurs in approximately 20% of metastatic breast cancers and is associated with more aggressive cancer and poor prognosis [274]. Trastuzumab is a recombinant monoclonal antibody that was developed to target HER2 and block growth and survival of HER2-dependent tumors. The addition of trastuzumab to chemotherapeutic regimens to treat breast cancer significantly slows the progression of breast cancer in women with HER2-positive tumors, with treatment effects positively correlated with the degree of HER2 overexpression [275]. Thus, testing to confirm HER2 overexpression is necessary before trastuzumab use. Although the data are conflicting and require further confirmation, a genetic association between HER2 655 A >G (Ile/Val) polymorphism (rs1136201) and trastuzumab cardiotoxicity has also been suggested [276].

The epidermal growth factor receptor (EGRF), also known as HER1 or ErbB1, is overexpressed in head and neck, colon, and rectal cancer. EGRF overexpression is associated with cancer growth and invasion and portends a poor clinical prognosis. The discovery of the *EGRF* gene and its role in cancer prognosis led to the development of EGRF antagonists, including cetuximab, panitumumab, erlotinib, and gefitinib. Cetuximab is a recombinant monoclonal antibody that binds to the extracellular domain of the EGFR, thus preventing epidermal growth factor and other ligands from activating the receptor. Cetuximab is indicated in the treatment of metastatic

TABLE 1.5 Consequences of Selected Genetic Variation in Drug Disposition and Drug Target Proteins

Gene	Drug Examples	Clinical Consequence
CYP2D6	Atomoxetine	PMs may have 10-fold greater atomoxetine exposure
	Codeine	UMs are at increased risk for morphine toxicity (details in Table 1.2)
CYP2C9	Warfarin	CYP2C9 deficiency increases bleeding risk
CYP2C19	Clopidogrel	CYP2C19 deficiency reduces drug effectiveness
G6PD	Rasburicase	G6PD deficiency increases risk for hemolytic anemia
TPMT	Azathioprine, 6-mercaptopurine, Thioguanine	Nonfunctional genotype increases the risk of serious, life-threatening myelosuppression with conventional drug doses
UGT1A1	Irinotecan	Reduced function genotype increases risk for drug-induced neutropenia
DPD	Capecitabine, 5-fluorouracil	DPD deficiency may lead to severe diarrhea, neutropenia, neurotoxicity)
SLCO1B1	Simvastatin	Increased risk for myopathy
DRUG-TARGET GENES		
EGFR	Cetuximab, Panitumumab	Determines drug effectiveness
HER2	Trastuzumab	Determines drug effectiveness
ADRB1	β-blockers	Influences variability in blood pressure response and possibly mortality reduction
VKORC1	Warfarin	Determines dose needed for optimal anticoagulation
KCNJ11 and *ABCC8*	Sulfonylureas	Drug effectiveness
KCNMB1	Verapamil	Possibly determines reduction in blood pressure
DRD3	Antipsychotics	Risk for tardive dyskinesia
GRK5	β-blockers	Drug effectives on clinical outcomes in heart failure
ATM	Metformin	Antidiabetic response
SLC6A4	SSRIs	Drug effectiveness
HTR2A	Clozapine	Drug effectiveness

colorectal cancers that overexpress EGRF, in which it has been shown to improve survival [277,278]. Similar to cetuximab, panitumumab is a monoclonal antibody that blocks activation of the EGRF and is indicated in metastatic colorectal cancer that progresses despite chemotherapy with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens. Erlotinib and gefitinib also target the EGRF and are indicated in nonsmall cell lung cancer.

Other examples of targeted chemotherapy developed based on genetic abnormalities include:

- rituximab, a monoclonal antibody used to treat CD20-positive, B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia;

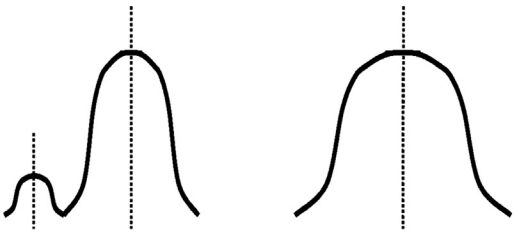

FIGURE 1.3 Many drug-metabolizing enzyme polymorphisms are inactivating resulting in distinct phenotypes, such as the poor metabolizer and extensive metabolizer phenotypes. In contrast, drug-receptor polymorphisms tend to be more subtle and help explain variability across single distribution curve.

- imatinib mesylate, a kinase inhibitor developed to block the product of a reciprocal translocation between chromosomes 9 and 22, occurring in 95% of patients with chronic myeloid leukemia; and
- crizotinib, an anaplastic lymphoma kinase (ALK) and c-ros oncogene1, receptor tyrosine kinase (ROS-1) inhibitor that targets the echinoderm microtubule associated protein like 4–anaplastic lymphoma kinase (EML4-ALK) gene fusion product in nonsmall-cell lung cancer.

Drug Target Receptor Genes in Cardiology

β_1-receptors are located in the heart and kidney, in which they are involved in the regulation of heart rate, cardiac contractility, and plasma renin release. β_1-receptor mediated effects contribute importantly to the pathophysiology of numerous cardiovascular diseases, including hypertension, coronary artery disease, and heart failure. In particular, plasma renin release and activation of the renin-angiotensin-aldosterone system lead to increased blood volume and vasoconstriction in hypertension. Increases in heart rate and cardiac contractility increases myocardial oxygen demand, thus contributing to myocardial ischemia in patients with coronary heart disease. Furthermore, increased sympathetic nervous system activity is one of the primary mechanisms contributing to cardiac remodeling and heart failure progression. Consequently, β-blockers exert beneficial effects across cardiovascular diseases, resulting in blood pressure reduction in hypertension, lowering of myocardial oxygen demand in ischemic heart disease, and attenuation of cardiac remodeling in heart failure. There is evidence that genetic variation for the adrenoceptor β-1 (ADRB1) may influence the effectiveness of β-blocker therapy.

The ADRB1 is encoded by an intronless gene, located on chromosome 10q24-26. Two common nonsynonymous SNPs in the *ADRB1*, p.S49G and p.R389G are in strong LD. The S49G SNP is located in the extracellular region of the receptor near the amino terminus, and the R389G variant is located in the cytoplasmic tail in the G-protein coupling domain of the ADRB1. In vitro studies show lesser receptor downregulation with the S49 form of the receptor and both greater receptor coupling to the G-protein and greater adenylyl cyclase activity with the R389 form [279,280]. There are ethnic differences in the S49G and R389G allele frequencies, with a G49 frequency of 12%–16% in Caucasians and 23%–28% in African Americans and a G389 frequency of 24%–34% in Caucasians and 39%–46% in African Americans [281].

The *ADRB1* gene has been the primary focus of research into genetic determinants of responses to *β*-blockers in hypertension, coronary heart disease, and heart failure [282–284]. In each case, the R389 allele or S49-R389 haplotype has been associated with greater response to β-blockade presumable because of greater adrenergic activity with this allele and haplotype. For example, treatment of hypertension with metoprolol produced greater blood pressure reduction in patients who were homozygous for the S49-R389

haplotype than in carriers of the G49 or G389 allele [285]. Among patients with coronary heart disease, the S49-R389 haplotype was associated with an increased risk for death compared to other haplotypes, an effect negated by treatment with atenolol [286]. In patients with heart failure, the homozygous R389 genotype was associated with greater improvements in left ventricular ejection fraction with carvedilol or metoprolol and greater survival benefits with bucindolol [287–289]. These clinical data are consistent with the in vitro data implying greater agonist-mediated effects (e.g., greater sympathetic nervous system-driven hemodynamic effects) with the S49 and R389 alleles and suggest that *ADRB1* genotype is an important determinant of blood pressure and cardiac responses to β-blockers.

The *ADRB1* genotype is also associated with β-blocker tolerability in heart failure. β-blockers are indicated for patients with heart failure because they attenuate the detrimental effects of the sympathetic nervous system on heart failure progression. However, because β-blockers have negative inotropic effects (i.e., reduced cardiac contractility), they can worsen heart failure when first started. For this reason, they must be started in very low doses with careful uptitration. Although most heart failure patients tolerate β-blocker initiation at low doses and slow uptitration, some experience significant heart failure exacerbation. The influence of *ADRB1* genotype on tolerability to β-blocker initiation and up-titration has been examined, and it was found that carriers of the Gly389 allele or the 49Ser/Ser genotype more frequently require increases in concomitant heart failure therapy (predominately diuretics) for management of symptoms of worsening heart failure during β-blocker titration than patients with other genotypes [290].

Stimulation of the presynaptic adrenergic alpha2C-receptor (ADRA2C) results in inhibition of norepinephrine release, and has been correlated with β-blocker response. The *ADRA2C* Del322-325 (α_{2Cdel}322-325) polymorphism causes an inframe deletion of 12 nucleic acids, resulting in the loss of four amino acids in the ADRA2C protein and loss of protein function. Loss of ADRA2C function would be expected to result in less inhibition of norepinephrine release, and consequently increased norepinephrine levels and sympathetic tone. The frequency of the Del322-325 variant exhibits marked variability by ancestry, with a frequency of approximately 0.40 in African Americans and <0.05 in those of European descent [291], and homozygosity for Del322-325 variant has been associated with higher risk of heart failure in African Americans compared to Caucasians.

In a large, multicenter, randomized, placebo-controlled heart failure trial, investigators found that individuals with the Del322-325 allele had greater reductions in sympathetic activity with bucindolol, a nonselective β-blocker with α1-receptor blocker properties. However, individuals with the wild-type (Ins322-325) *ADRA2C* genotype derived significant survival benefits from bucindolol, whereas Del322-325 allele carriers did not [292]. The mechanism underlying this association was not determined. However, it was hypothesized that the significant sympatholytic activity with bucindolol in Del322-325 allele carriers caused detrimental clinical effects. These findings might explain the negative association between bucindolol use and heart failure survival in the study population overall. Specifically, whereas carvedilol, metoprolol, and bisoprolol were all shown to improve survival in heart failure, bucindolol was not [293,294]. However, compared to other β-blocker trials, the trial with bucindolol enrolled a large number of African Americans, in whom the Del322-325 allele, associated with lack of benefit with bucindolol, is ten-times more common.

With its pharmacological targets at the ADRB1 on myocytes and on the adrenergic neurons, the interaction of both *ADRB1* and *ADRA2C* SNPs could further modulate the drug response. A recent clinical trial identified subsets of populations with different responses based

on evaluation of both genotypes. Enhanced bucindolol efficacy was associated with *ADRB1* homozygotes, whereas intermediate efficacy was observed in patients with Gly variant of the *ADRB1* SNP and homozygote carriers of the wild-type α_{2C}322-325. In contrast, a lack of efficacy was reported in carriers of the *ADRB1* Gly variant and homozygous carriers of the Del322-325 allele [295]. Similarly, Reddy et al. recently reported that in children with dilated cardiomyopathy, β-blockers produced better hemodynamics and preservation of cardiac function in those with high-risk genotypes, including α_{2Cdel}322-325 and β_1Arg389 [296]. Similar combinatorial pharmacogenomic approaches have also been investigated in psychopharmacology and is discussed in Chapter 7.

Drug Target Genes in Psychiatry

Antidepressants target 5-hydroxytryptamine (5-HT) receptors, and a number of studies have examined the association between antidepressant treatment response and 5-HT genotype, as described in more details in Chapter 7. However, results of these studies are largely inconsistent and even conflicting. For example, in a large-scale association study of 68 candidate genes, only the synonymous IVS2 A/G (rs7997012) SNP within intron 2 of the *HTR2A* gene, which codes for the postsynaptic 5-HT_{2A} receptor, was associated with response to citalopram [297]. Although a large study in European Caucasians confirmed the association between the rs7997012 SNP and antidepressant response, the findings were opposite of those in the initial study [298].

The majority of drug-target genetic associations discussed so far related to drug effectiveness. Variation in the *DRD3* gene, encoding for the dopamine D3 receptor, is an example of drug-target genotype linked to adverse drug effects. Specifically, the *DRD3* p.S9G variant has been implicated in risk for developing tardive dyskinesia, an irreversible movement disorder that develops after long-term antipsychotic treatment, particularly with typical antipsychotics. In a meta-analysis, the G9 allele was significantly overrepresented among 317 patients with tardive dyskinesia compared to 463 patients without this adverse drug effect [299]. Furthermore, G9 allele homozygotes had higher abnormal involuntary movement scores compared to both heterozygotes and S9 allele homozygotes. This association was confirmed in another meta-analysis [300].

Drug Target Genes in Pain Management

Over the years, several SNPs have been discovered for genes that encode different analgesic drug targets, and association studies had been carried out in various pain phenotypes. Not surprisingly, nonreplication of findings is common. The μ–opioid receptor (MOR) is the primary drug target for endogenous opioid peptides and the opioid analgesics. With more than 100 variants of the μ–opioid receptor gene *(OPRM1)* identified [301], the most studied polymorphism is the c.118A>G (rs1799971) SNP in exon 1 of *OPRM1* that results in p.N40D, and lower mRNA expression and protein amount associated with the G allele. This functional difference between the two alleles is reflected in stronger binding by the G allele to the endogenous opiate β-endorphins, thereby affecting opioid action at the receptor site, with decreased opioid potency by a factor of two to three [302]. This is evident by the report of Oertel et al., who showed that despite a stronger binding, the signal efficacy is weaker in regions of the brain that are important to pain perception and experience [303].

Decreased clinical response to opioids had been shown in carriers of the G allele. Klepstad et al. reported morphine-dosage requirements in 207 cancer patients differed among carriers of the wild type versus that of the variant allele. Four homozygous carriers of the G allele

required 225 ± 143 mg/day for effective pain control compared to 97 ± 89 mg/day in 78 wild-type homozygotes ($P = .006$). However, dosage requirement for heterozygote was 66 ± 50 mg/day, so there was no evidence of a gene-dose effect [304]. Chou et al. also reported similar findings of different dosage requirements for postoperative pain with patient-controlled analgesia, at 24 and 48 h after total knee arthroplasty respectively, of 22.3 ± 10 mg and 40.4 ± 21 mg in homozygous carriers of the G allele versus 16 ± 8 mg and 25.3 ± 15.5 mg in wild-type homozygotes [305]. Two patients identified as "low" responders of morphine requiring 1.8 and 2 gm/day were identified as a carrier of the G allele [306,307]. These and other clinical trial results [308–312]suggest that *OPRM1* genotype and haplotype analyses could have clinical implication for pain control in a variety of patients. Chidambaran et al. also reported a higher risk of morphine-induced respiratory depression associated with the A118G SNP [312].

In addition to morphine, a significant association has also been shown between the A118G SNP and decreased potency of morphine-6-glucuronide (M6G), the pharmacologically active metabolite of morphine. Using pharmacokinetic–pharmacodynamic modeling, the study showed that the effector site EC_{50} for M6G was 714 ± 197 nmol/L in six homozygous carriers of the wild-type, 1,475 ± 424 nmol/L in five heterozygotes, and 3,140 nmol/L in a homozygous carrier of the G allele [313]. Additional studies have reported decreased effect and higher-dosage requirement for other opioid agonists, including fentanyl and alfentanil, in carriers of the G allele [309,314–318]. However, negative association with A118G SNP has been reported for fentanyl, which was attributed by the investigators to the small sample size of the study [319]. In view of the low frequency of A118G SNP, the issue of small sample size with associated low statistical power to detect difference in analgesic doses and/or outcome is important.

Signal Transduction Proteins

Signal transduction encompasses the cascade of events following drug binding to a receptor that ultimately leads to a change in cellular response. G-protein receptor kinase 5 (GRK5) is an example of a signal transduction protein linked to drug response. The ADBR1 and other adrenergic receptors are coupled to GTP-binding proteins also called G-proteins. Upon ligand binding, the receptor couples to the intracellular G-protein to elicit a cellular response. GRKs phosphorylate cardiac receptors, essentially inhibiting receptor-mediated signaling and, thus, serving in a manner analogous to natural β-blockade. The *GRK5* p.Q41L polymorphism occurs commonly in African Americans, with an allele frequency >30%. However, it rarely occurs in Caucasians. The L41 allele has been found to more effectively uncouple agonist-mediated receptor signaling and has been associated with increased transplant-free survival in African Americans with heart failure [320]. Patients with the L41 allele derived no benefit from β-blocker therapy, presumably, because they already have inherent downregulation of ADRB1 receptor signaling [321]. However, in patients with the *GRK5* 41QQ genotype, which is associated with a poor prognosis, treatment with β-blocker therapy significantly improved transplant-free survival [320].

The dopamine and serotonin receptors targeted by antipsychotics are also G-protein-coupled receptors (GPCRs) and signal to effector proteins through intracellular G-protein subunits. Regulators of G-protein signaling shorten the duration of neurotransmitter-mediated receptor signaling through the GPCRs. The regulator of G-protein signaling 4 (RGS4) is one such regulator, and it regulates the activity of the GPCRs. The gene that encodes RSG4 had been identified as a vulnerability gene for schizophrenia [322,323]. and variants of *RSG4* have been studied as predictors for antipsychotic treatment response.

Three SNPs of *RSG4* have been reported to confer differential treatment responses in three ethnic groups. In patients of African descent, those with the CC genotype of the rs951439 SNP had longer (391 days) and better (21% improvement based on the Positive and Negative Syndrome Scale [PANSS]) response to perphenazine than ziprasidone (124 days and 5% worsening, respectively). On the other hand, the same patient population with the TT genotype of the rs2842030 SNP responded better to perphenazine (24% improvement in the PANSS) than to quetiapine, risperidone, and ziprasidone. A sharp contrast in association was shown in patients with European descent, in which risperidone treatment resulted in better response with the TT genotype of the rs951349 SNP and GG genotype of the rs2842030 SNP [324]. In 120 schizophrenic patients of Chinese descent, rs2661319 of *RSG4* was found to predict response to risperidone treatment [325]. These data with *RSG4* polymorphisms underscore the importance of patient population stratification by ethnicity in pharmacogenomics investigations. It is also noteworthy that the investigators of the Chinese study also had reported in other studies that polymorphisms affecting the dopamine D_2 receptor (Ser311Cys), D_3 receptor (Ser9Gly), and 5-HT2A receptor (102-T/C) predict treatment response to risperidone [326–328]. Whether evaluating a combination of SNPs could result in better response prediction remains to be investigated.

The alpha adducin (ADD1) gene encodes for α-adducin, a cytoskeletal protein involved in signal transduction and renal sodium transport. The *ADD1* p.G460W variant is associated with greater renal sodium–potassium pump activity, renal sodium retention, and salt-sensitive hypertension [329,330]. Given its role in regulating sodium reabsorption and potentially mediating increased hypertension risk, the *ADD1* gene has been studied for its contribution to diuretic response. Although the 460W allele has been linked to greater blood pressure reduction with thiazide diuretics, the data are inconsistent [329,331]. The *ADD1* gene appears to interact with other genes involved in renal sodium reabsorption, including the neural precursor cell expressed, developmentally downregulated 4-like (NEDD4L) and lysine-deficient protein kinase 1 (WNK) genes [329]. This may explain the inconsistencies in the data when *ADD1* is analyzed alone rather than in the context of other genes involved in renal sodium handling, and illustrates the likely contribution of multiple genes to the efficacy of many drugs.

Enzyme Genes

VKORC1 is the target site for warfarin. Specifically, warfarin inhibits VKORC1 to prevent regeneration of a reduced form of vitamin K necessary for clotting factor activation. Two common variants, -1639G>A (rs9923231) and -1173C>T (rs9934438) in the *VKORC1* regulatory regions, are associated with reduced gene expression [332]. The frequency of 1639A allele of rs9923231 is highest in Asians (~90%) and lowest in persons of African descent (10%), with an intermittent frequency in populations of European descent (~40%) [333].

Numerous studies have documented the association between *VKORC1* genotype and warfarin-dose requirements. The -1639AA, AG, and GG genotypes are associated with average warfarin-dose requirements of approximately 3, 5, and 6 mg/day, respectively. The two SNPs are equally predictive for predicting warfarin-dose requirement. Recent data suggest that dosing based on one of the *VKORC1* SNP, in addition, to *CYP2C9* genotype, leads to more accurate dose prediction and may reduce the risk for adverse clinical outcomes early in the course of warfarin therapy [334,335]. The VKORC1 genotype is described in detail in Chapter 6.

The angiotensin-converting enzyme (ACE) gene has been widely studied for its effects on ACE inhibitor response. An insertion/deletion

(I/D) polymorphism in intron 16 of the *ACE* gene results in the presence or absence of a 287-base-pair fragment. The *ACE* D allele has been linked consistently to higher plasma concentrations of ACE, the enzyme responsible for the conversion of angiotensin I to the potent vasoconstrictor angiotensin II [336]. Given its association with ACE concentrations, a number of investigators have examined whether the I/D polymorphism contributes to the interpatient variability in ACE inhibitor response. However, much of the data with the I/D polymorphism and blood pressure response to ACE inhibitors are inconsistent and even conflicting, with some studies demonstrating greater response with the *D/D* genotype, whereas others have shown greater response with the *I/I* genotype, and further studies showing no association. In one of the largest pharmacogenetic studies to date, including nearly 38,000 patients, there was no association between the *ACE I/D* genotype and either blood pressure response or cardiovascular or renal outcomes with antihypertensive therapy [337].

Numerous polymorphic proteins are involved in the complex signaling pathway of the renin–angiotensin system, including renin, angiotensinogen, the angiotensin II type 1 receptor, bradykinin, and aldosterone synthase. Thus, a likely explanation for the inconsistent data with the *ACE* gene and ACE inhibitor response in hypertension is that a single polymorphism provides minimal contribution to ACE inhibitor response. Rather, ACE inhibitor response may be best determined by a combination of multiple polymorphisms occurring in multiple genes involved in the renin–angiotensin pathway.

The data with the *ACE I/D* genotype and ACE inhibitor response in patients with heart failure are more compelling. In this population, the *ACE* D allele has been associated with an increased risk for cardiac transplant or death [338–342]. As described in detail in Chapter 6, the detrimental effect of the *ACE* D allele on transplant-free survival appears greatest among patients who are taking lower than recommended doses of ACE inhibitors. These data suggest that maximizing the ACE inhibitor dose may be necessary in *ACE* D allele carriers to attenuate the harmful effects of this allele [342,343].

Metformin is an antidiabetic drug that works in part by activating adenosine monophosphate-activated protein kinase (AMPK), which is a master regulator of cell and body energy homeostasis and glucose uptake in skeletal muscle [344]. The ataxia-telangiectasia mutated (ATM) is a DNA repair gene that acts upstream of AMPK and appear necessary for metformin action [345]. A GWAS identified a significant association between metformin response in type 2 diabetic patients and a polymorphism in a locus containing the *ATM* gene [345]. The potential significance of ATM for metformin response is further described in Chapter 9.

The catecho-O-methyltransferase (COMT) enzyme is a key modulator of the adrenergic and dopaminergic systems, which play a role in pain modulation. A functional SNP in the *COMT* gene, c.472G>A (rs4680), results in a p.V158M substitution with three-to four-fold decrease in enzyme activity. The reduced enzyme activity leads to decreased dopamine degradation and subsequent increases in norepinephrine and epinephrine levels that may be associated with exaggerated levels of pain [346]. Down regulation of endorphins with compensatory upregulation of MOR has also been suggested to be a result of the SNP [347,348]. Cancer patients who are homozygous carriers of the M variant (high pain-sensitivity patients) reportedly required more morphine (155 ± 160 mg/day) than heterozygotes (117 ± 10 mg/day) and homozygous carriers of the wild-type V allele (95 ± 99 mg/day) [349]. These results were replicated in a later study [350]. Reyes–Gibby et al. also reported higher morphine-dosage requirement: 63% and 23%, respectively, for satisfactory pain control in patients with the *COMT Val/Val* and *Val/Met* genotypes compared to carriers of

Met/Met genotype ($P = .02$) [311]. The increased morphine toxicity reported in the patient by Madadi et al. had a *COMT* haplotype CCG (rs4633, rs4818, rs4680) and a *G/G* genotype for the *OPRM1* (rs1799971, A118G) SNP, in addition, to the *ABCB1* haplotype [186]. This again highlights the importance of multiple genes in mediating drug disposition and effect and the need of genotyping multiple functional polymorphisms in pharmacogenomic studies. Interestingly, in addition to reporting negative association for the *OPRMI* A118G (rs1799971) polymorphism that was discussed in the section on drug-target genes in patient management, Landau et al. also did not find a correlation between fentanyl therapeutic outcomes with *COMT* genotype [319].

Ion Channel Genotype

One of the most often cited examples of ion channel genes with consequences for drug response are genes for the pore-forming channel proteins that affect potassium and sodium transport across the cardiac cell membrane. Mutations in cardiac ion channel genes predispose individuals to congenital long-QT syndrome. Moreover, there is evidence that these mutations may increase the risk for drug-induced torsades de pointes [351,352]. This is discussed in detail in Chapter 6.

The large-conductance calcium and voltage-dependent potassium (BK) channel is another example of an ion channel with genetic contributions to drug response. The BK channel is found in vascular smooth muscle and consists of pore-forming-α and regulatory-β1 subunits. The β1 subunit enhances calcium sensitivity and decreases smooth muscle cell excitability, thus attenuating smooth muscle contraction. The *KCNMB1* gene encodes for the BK channel β1 subunit. A common SNP in the *KCNMB1* gene, Glu65Lys, results in a gain of function of the channel and increased calcium sensitivity compared to the wild type [353]. Given its role in mediating calcium sensitivity, the *KCNMB1* gene was examined for its effect on response to the calcium channel blocker, verapamil. Among patients with hypertension and coronary heart disease who were started on verapamil, 65Lys allele carriers achieved blood pressure control more rapidly than 65Glu homozygotes, suggesting that the Glu65Lys SNP enhances response to calcium channel blockers and contributes to the interpatient variability in blood pressure reduction during calcium channel blocker therapy [354].

The epithelial sodium channel (ENaC) is another example of an ion channel with genetic contributions to drug response. The ENaC is located in the distal renal tubule and collecting duct of the nephron and serves as the final site for sodium reabsorption. The channel is composed of α, β, and γ subunits, encoded by the *SCNN1A*, *SCNN1B*, and *SCNN1G* genes, respectively. In a healthy volunteer study, SNPs in the *SCNN1B* and *SCNN1G* genes were associated with natriuretic and diuretic responses to single oral doses of loop diuretics. Loop diuretics are commonly prescribed for managing symptoms of fluid overload in heart failure. Whether genes encoding for ENaC subunits influence response to loop diuretics in heart failure remains to be determined. But, given the significant consequences of under- or overdosing loop diuretics in this disease, such information could have significant clinical value.

The potassium inwardly rectifying channel, subfamily J, member 11 gene (KCNJ11) and the sulfonylurea receptor gene (ABCC8) encode the Kir6.2 and sulfonylurea receptor-1 (SUR1) subunits of pancreatic ATP-sensitive potassium (K_{ATP}) channels, respectively. Activating mutations in the *KCNJ11* and *ABCC8* cause K_{ATP} channels to remain open, which promotes hyperpolarization of the pancreatic β cell membrane and impaired insulin release [355,356]. Sulfonylurea drugs promote K_{ATP} channel closure, thereby attenuating the effects of activating mutations in *KCNJ11* and *ABCC8*. As such, sulfonylureas are especially

effective in patients with *KCNJ11* or *ABCC8* activating mutations [356,357]. Chapter 9 provides a more detailed discussion of these genetic variations and their effects on response to sulfonylurea agents.

CONCLUSION

Variations in genes influencing drug pharmacokinetics and pharmacodynamics often jointly influence drug response, as is the case with warfarin, the dose requirements for which are influenced by both the *CYP2C9* and *VKORC1* genotypes. Thus, when taking a candidate gene approach to discovery of variants impacting drug response, genes encoding proteins involved in determining drug bioavailability (transporter proteins, drug metabolizing enzymes) and response (receptor, enzyme, ion channel, and/or intracellular signaling proteins) should be considered. Genome-wide approaches to identifying determinants of drug response may reveal previously unknown proteins involved in eliciting drug response that represent potential biomarkers for predicting drug effectiveness or risk for toxicity. In addition, proteins involved in disease pathophysiology may represent attractive targets for drug development, as most often demonstrated in the area of oncology.

QUESTIONS FOR DISCUSSION

1. What are examples of drug metabolism and drug-transporter genotypes that affect drug response?
2. What are examples of drugs developed based on an understanding of genes involved in disease pathophysiology.
3. What are examples of drug-target genes with implications for drug response?
4. How might genes for drug metabolism, drug transport, and/or drug-target sites jointly influence drug response?

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