Clinically Relevant Genetic Variations in Drug Metabolizing Enzymes

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Abstract

In the field of pharmacogenetics, we currently have a few markers to guide physicians as to the best course of therapy for patients. For the most part, these genetic variants are within a drug metabolizing enzyme that has a large effect on the degree or rate at which a drug is converted to its metabolites. For many drugs, response and toxicity are multi-genic traits and understanding relationships between a patient's genetic variation in drug metabolizing enzymes and the efficacy and/or toxicity of a medication offers the potential to optimize therapies. This review will focus on variants in drug metabolizing enzymes with predictable and relatively large impacts on drug efficacy and/or toxicity; some of these drug/gene variant pairs have impacted drug labels by the United States Food and Drug Administration. The challenges in identifying genetic markers and implementing clinical changes based on known markers will be discussed. In addition, the impact of next generation sequencing in identifying rare variants will be addressed.

Keywords

Adverse drug reactions; Cytochrome P450; drug metabolizing enzymes; pharmacogenetics; pharmacogenomics; single nucleotide polymorphisms

INTRODUCTION

Differences in response to medications have long been recognized by physicians, but it was not until 1957 that Arno Motulsky used previously published works on variations in drug response to propose that "...hereditary gene-controlled enzymatic factors determine why, with identical exposure, certain individuals become 'sick,' whereas others are not affected" [1]. Two years later, Vogel first coined the term "pharmacogenetics" to describe the relationship between genetic factors and response to medications [2]. Advances in biochemistry allowed for the discovery of drug metabolizing enzymes and characterization of the various reactions they catalyzed while advances in molecular genetics allowed for an improved understanding of both the DNA sequence responsible for the production of these

CONFLICTS OF INTEREST

enzymes and the consequence of genetic variation in that sequence on enzyme activity. The goal of pharmacogenetics is to use genetics to predict response to therapy and to tailor medications appropriately. More recently, there has been a shift from studying variants within one or more candidate genes (pharmacogenetics) towards evaluating the entire genome for associations with pharmacologic phenotypes (pharmacogenomics). This review will focus on the clinically relevant consequences of common genetic variation on drug metabolizing enzymes and the consequences of drug metabolism. Special attention will be paid to the variants that produce predictable changes in drug metabolism and have impacted clinical practice and/or regulatory labeling. Finally, newer approaches to understanding the interplay between genetic variation and drug response as well as the future of "personalized medicine" will be discussed.

DRUG METABOLISM

Drug metabolism is typically responsible for converting drugs to compounds that are more water soluble and more easily excreted but may also be involved in the conversion of prodrugs into active compounds or conversion of drugs to toxic metabolites [3]. Although there are considered two pathways of metabolism: the phase I reactions (oxidation, reduction and hydrolysis) and the phase II conjugation reactions (glucuronidation, acetylation, sulfation and methylation) [3], this classification is historical, and does not necessarily refer to the order of reactions in drug metabolism. Ultimately, all reactions serve the same general purpose of converting lipophilic drugs into hydrophilic metabolites for excretion [3].

There is a rapidly expanding list of genetic variants that affect the function of drug metabolizing enzymes and lead to altered drug responses. Clinicians are becoming increasingly aware of the impact of genetic variation on the therapeutic index of a given medication. Although there are a number of associations identified between drugs and their respective drug metabolizing enzyme, we have chosen to focus on the drug-variant combinations that should merit special consideration by clinicians at this time.

THE PHASE I ENZYMES

The vast majority of phase I reactions are catalyzed by the cytochrome P450 superfamily of hemoproteins. Early studies of drug metabolism demonstrated the NADPH-dependent oxidation of various compounds by liver microsomes [4,5], and the enzyme responsible for this oxidation was later described as an iron-containing molecule having an absorbance peak of 450 nm, hence cytochrome P450 [6]. Evidence for hydroxylase activity of P450 [7] as well as its role in the metabolism of commonly prescribed drugs like codeine [8] soon followed. Initially assumed to be one enzyme, evidence for multiple isoforms began to emerge in the late 1960s [9,10], and the first experiments to isolate and purify these isoforms from animal liver microsomes emerged in the late 1970s [11] and early 1980s [12]. As more and more isoforms emerged, a recommended nomenclature system was developed where gene families were represented by Roman (later changed to Arabic [13]) numerals, subfamilies represented by letters and individual genes represented by Arabic numerals [14]. The explosion of knowledge of human genetic variation from the sequencing of the human genome has necessitated another addition to the P450 nomenclature: a star (*) followed by a unique Arabic numeral is used to denote nucleotide changes in the reference sequence, which is usually denoted by -*1 [15]. Comprehensive databases of P450 variation are available online courtesy of the Human Cytochrome P450 Nomenclature Committee at http://www.cypalleles.ki.se and the Pharmacogenetics Knowledge Base at http://www.pharmgkb.org. A similar nomenclature has been adopted for the other phase I and phase II enzymes [16-21]. The P450 enzyme families involved with the majority of drug metabolism in humans are *CYP3A*, *CYP2D*, and *CYP2C*. The relative abundance of the P450

enzymes in the human liver and the percentage of drugs these enzymes metabolize are outlined in Fig. (**1**).

CYP2D6

CYP2D6 has the largest phenotypic variation of the P450 enzymes, and some of the earliest observations of variations in drug metabolism have now been linked to polymorphisms in this gene. In the 1970's, groups investigating the metabolism of two new drugs, sparteine and debrisoquine, both found that a significant minority of individuals were unable to metabolize these drugs [22,23]. Later investigators were able to show that the inability to metabolize these drugs was a recessive trait [24]; was present in approximately 5-10% of Europeans; and that the inability to oxidize sparteine was associated with the inability to hydroxylate debrisoquine [25], suggesting that metabolism of these two drugs was by the same enzyme. It became evident that this deficiency also affected the metabolism of other drugs [26], and that it was at least partially responsible for previous observations that nortryptyline plasma steady state concentrations were influenced by genetics [27,28]. Introduction of molecular techniques in the 1990s allowed for the sequencing of patients with the 2D6 poor metabolizer phenotype and recognition of several variations in the sequence of *CYP2D6* [29-31] as well as the functional consequences of these variants on gene expression [32]. Further identification of patients with an ultrarapid metabolism of CYP2D6 substrates due to duplicated or multiple extra copies of a functional *CYP2D6* gene [33] and higher levels of enzyme expression led to the current allelic dosage model of CYP2D6 metabolism: where poor metabolizers are homozygous or compound heterozygotes for various loss-of-function alleles, intermediate metabolizers carry one defective allele, normal metabolizers carry zero defective alleles, and extensive metabolizers have a gain in 2D6 function due to duplicated or multiple extra copies of a functional *CYP2D6* gene.

CYP2D6 is responsible for the metabolism of 25-30% of prescription medications, but represents about 2-5% of total CYP content of the liver [34]. It is also present in small amounts in the brain [35], gastrointestinal tract [36] and lungs [37]. That genetics plays such a large role in determining inter-individual variation in 2D6 metabolism may be due to the fact that it is thought to be the only non-inducible P450 in humans [38]. There are over 80 allelic variants in *CYP2D6,* but most are quite rare. Important variants include *CYP2D6*9*, *CYP2D6*10*, *CYP2D6*17*, *CYP2D6*29*, and *CYP2D6*41* which have decreased catalytic activity (intermediate metabolizer phenotype); *CYP2D6*3* through *CYP2D6*8* as well as *CYP2D6*36* which have no functional activity (poor metabolizer phenotype); and duplications of *CYP2D6*1xN*, *CYP2D6*2* or *CYP2D6*35* which lead to enhanced functional capacity and the ultrarapid metabolizer phenotype [39]. The distribution of poor, intermediate, extensive and ultrarapid CYP2D6 metabolizers varies among ethnic groups. For example, the reduced-function *10 allele is observed in about 38% to 50% of East Asians but only about 3% of Caucasians and 6% of Africans. Likewise, the reduced-function *17 allele is present almost exclusively in Africans (approximately 21%). The normal-function *2 allele (extensive metabolizer phenotype), in contrast, is present in about 25% of Caucasians and 31% of Africans but only 10% to 12% of East Asians [40]. These differences likely account for some of the ethnic variation in response to medications that are CYP2D6 substrates [41-43].

One of the most publicized examples in pharmacogenetics has been on the effect of variation in *CYP2D6* on clinical outcome relates to the use of tamoxifen in the treatment of estrogen-receptor positive breast cancer. The metabolism of tamoxifen is complex, but CYP2D6 mediates the conversion of tamoxifen to endoxifen (4-hydroxy-*N*-desmethyltamoxifen), a metabolite with a much more potent estrogen receptor binding capacity than the parent compound [44]. Because 2D6 activity is so variable and is the major enzyme responsible for endoxifen production, there has been great interest in the impact of

2D6 variation on response to tamoxifen therapy in women with breast cancer. Most of these studies have been retrospective and represent a heterogeneous patient population using various tamoxifen doses for either adjuvant therapy or chemoprevention of recurrence. Although results are quite contradictory, there have been several series where patients treated with tamoxifen that have a CYP2D6 poor metabolizer phenotype have lower circulating levels of endoxifen and likely have an increased risk of relapse [45-49]. Similarly, patients on tamoxifen treated with medications that act as potent 2D6 inhibitors, like the use of paroxetine to prevent tamoxifen-induced hot flashes, may also have an increased risk of breast cancer recurrence [47,50,51]. Because of the lack of concordant, prospective data, the adoption of routine *CYP2D6* genotype testing in women with early breast cancer has not been routinely adopted in clinical practice. However, direct-to-consumer genetic testing of *CYP2D6* variants is now commercially available and may influence a patient's decision to start tamoxifen therapy.

A striking example of the impact of genetic variation on response to medication came with the unfortunate report of a fatal opioid overdose in a breastfeeding neonate [52]. An estimated 40% of postgestational women are prescribed codeine for the pain associated with childbirth [53], and its use is generally considered safe in breastfeeding mothers based on several studies finding only low levels of codeine excreted in breast milk [54-56]. However, in the case of the neonate described above, the child's mother was an ultrarapid CYP2D6 metabolizer, and therefore likely had a rapid conversion of codeine to its active metabolite, morphine. The infant was noted to have progressive lethargy prior to being found unresponsive on day of life 11, and a postmortem examination revealed a markedly elevated serum morphine concentration [52]. A subsequent case-control study demonstrated that breastfed infants of CYP2D6 ultrarapid metabolizers were much more likely to experience central nervous system depression when their mothers were prescribed codeine [53].

CYP2C19

The same approaches used to discover *CYP2D6* polymorphisms were employed to investigate individuals who were unable to metabolize the anticonvulsant *S*-mephenytoin [57]. Poor metabolizers of *S*-mephenytoin were hypothesized to have a different defect than sparteine or debrisoquine poor metabolizers, as these two traits did not co-segregate [57]. The gene for this enzyme was cloned in 1994, and is now referred to *CYP2C19* [58]. *S*-mephenytoin has been used extensively as a metabolic probe of CYP2C19 activity, and a marked ethnic difference in the poor metabolizer phenotype has been observed. While the poor metabolizer phenotype is only present in 2-6% of Caucasians, up to 20% of Asians are poor metabolizers [59].

Various sequencing technologies have identified nearly 30 allelic variants of *CYP2C19* [60]. Some of these alleles are associated with reduced catalytic activity (*CYP2C19*5* and *CYP2C19*8*) or no functional activity (*CYP2C19*2*, *CYP2C19*3*, *CYP2C19*4*, *CYP2C19*6* and *CYP2C19*7*) and a poor metabolizer phenotype, whereas others are associated with greater catalytic activity (*CYP2C19*17*) and an extensive metabolizer phenotype [39]. Several pharmacologic inhibitors of 2C19 exist: cimetidine, oral contraceptives, fluoxetine among others, and inhibition occurs in a gene dose-dependent fashion such that homozygous extensive metabolizers (*CYP2C19*17/*17*) experience the most 2C19 inhibition with these compounds, where homozygous poor metabolizers experience little to no inhibition [61]. This phenomenon is evident in the inhibition of phenytoin metabolism by compounds like fluoxetine or cimetidine, leading to increased phenytoin exposure and toxic side effects [62].

The impact of 2C19 metabolic variation has been highlighted by several studies and a meta-analysis in patients with coronary artery disease treated with the antiplatelet agent,

clopidogrel [63-66]. Clopidogrel is a prodrug which is oxidized to its active metabolite largely by CYP2C19. Patients with the *CYP2C19*2* allele, a G to A polymorphism at position 681 that leads to a splicing defect and a truncated protein, are less able to activate clopidogrel and are at higher risk of serious cardiovascular events. However, even in a genetically homogenous population, the effect of *CYP2C19* genotype on variability to clopidogrel response appears to be small [64]. In a separate analysis of over 1500 patients undergoing percutaneous coronary stent placement, patients with one or more *CYP2C19*17* alleles had a significant increase in bleeding complications, a phenotype consistent with extensive metabolism [67]. Despite the fact that *CYP2C19*2* genotype and other non-genetic factors only predict about 12% of the variability in clopidogrel response [68], in 2009 the United States Food and Drug Administration changed the label of clopidogrel to highlight the impact of *CYP2C19* genotype on clopidogrel pharmacokinetics and clinical response [65]. Prospective studies on the impact of other antiplatelet agents, such as prasugrel or using a higher dose of clopidogrel in 2C19 poor metabolizers with coronary artery disease are underway [69,70]. Recently, *in vitro* metabolomic studies have found that paraoxonase-1 (*PON1*) was the enzyme responsible for the majority of clopidogrel activation, and that a variant within the gene, Q192R, accounted for the majority of variability in drug biotransformation. These findings were confirmed in a clinical cohort, where the QQ192 homozygotes had a much higher rate of coronary stent thrombosis and lower concentrations of the active metabolite of clopidogrel when compared to RR192 homozygotes [71]. This example highlights one of the main difficulties of pharmacogenetic and genomic studies, where differences in phenotype endpoints and/or populations studied can lead to variable associations.

CYP2C9

CYP2C9 is responsible for the metabolism of several drugs with narrow therapeutic indices (i.e. phenytoin and warfarin) and is another human P450 with many functionally significant polymorphisms. It is also subject to both induction and inhibition by a variety of other drugs [39]. Approximately 1-2% of Caucasians have a poor metabolizer phenotype [72]. Up to 20% of Caucasians carry one *CYP2C9*2* allele, and 17% carry one *CYP2C9*3* allele, both of which have reduced function [72]. Interestingly, in Chinese individuals, *CYP2C9*2* is not present and *CYP2C9*3* is only present in 2-5% [73]. In African Americans, *CYP2C9*8* appears to be the most prevalent variant allele, and is likely the major contributor to CYP2C9 expression in this racial group [74,75].

Variations in 2C9 metabolism have had a large part in understanding the wide interpatient variability in dosing requirements of one of the most commonly prescribed anticoagulants, warfarin. Pharmacologic inhibition of 2C9 by drugs like fluconazole was known to influence the clearance of warfarin [76], and patients requiring a lower maintenance dose of warfarin to achieve therapeutic anticoagulation were 6 times more likely to have one or more *CYP2C9* variant alleles [72]. In this study, poor metabolizers were also much more likely to experience a major bleeding event while on warfarin [72]. Further studies attributed between 10-20% of the variability in warfarin dose requirement to *CYP2C9* genotype, and variation in a gene in the pharmacodynamic pathway of warfarin, *VKORC1*, was able to account for another 20-30% of the variability [77]. Two large prospective studies of pharmacogenetic-based dosing of warfarin based on *CYP2C9* and *VKORC1* genotype as well as other clinical factors (age, race, smoking, concomitant medications) are underway [78,79], and language regarding the impact of variation in *CYP2C9* and *VKORC1* on warfarin dosing has already been incorporated into the drug label [80].

CYP3A4/CYP3A5

CYP3A4 accounts for approximately 30% of hepatic P450 content and is involved in over 50% of drug metabolism, including immunosuppressants, chemotherapeutics, macrolide antibiotics, antidepressants, anxiolytics, antipsychotics, opiates, calcium channel blockers, and statins [39]. Despite considerable variation in levels of activity among individuals, *CYP3A4* does not appear to have polymorphisms that result in absence of functional protein. Several polymorphisms exist within the gene, and some of these do alter the catalytic activity of the enzyme, but these variations have not impacted clinical care to date. Wide variability in CYP3A4 activity is due in part to the large number of substrates capable of inhibiting or inducing the enzyme. Classic examples of 3A4 inducers include the enzyme-inducing antiepileptics phenobarbital, phenytoin, carbamazepine and oxcarbazepine; the non-nucleoside reverse transcriptase inhibitors efavirenz, nivirapine and etravirine; the herbal antidepressant St. John's Wort (hyperforin); as well as the antituberculosis agent rifampin [39]. Inhibitors include protease inhibitors (ritonavir, indinavir, nelfinavir), macrolide antibiotics (erythromycin, clarithromycin), grapefruit juice, and azole antifungals (fluconazole, ketoconazole, voriconazole) [39]. CYP3A4 is also highly expressed in the intestinal tract, and these enzymes can be inhibited and induced by the same substrates, altering the first pass effect [81]. Another factor in the wide interpatient variability in 3A4 activity is the variable expression of CYP3A5, a related enzyme with a broad overlap in substrate specificity with CYP3A4. Only 10% of Europeans express CYP3A5, mostly because of the *CYP3A5*3* variant which is an A to G polymorphism at position 6986 resulting in the creation of a new splice site and a truncated protein [82]. The proportion of CYP3A5 expressers is significantly higher in African Americans, due in large part to the rarity of the *CYP3A5*3* allele in this population [83]. Other polymorphisms (*CYP3A5*6* and *CYP3A5*7*) also result in abnormal splicing, and are the predominant polymorphisms in African Americans who do not express 3A5 [82].

Other P450 Enzymes—Several other P450 enzymes, including *CYP1A2*, *CYP2A6*, *CYP2B6* and *CYP2E1* are expressed in humans, but in total only account for 5-15% of drug metabolism (Fig. **1b**) [39]. Variations in activity can be the result of genetic polymorphisms for several of these enzymes, but their significance in clinical practice largely remains unclear. Some emerging examples include a reduced ability of patients carrying one or more *CYP2B6* variant alleles (*CYP2B6*6, CYP2B6*16* and/or *CYP2B6*18*) to activate the antineoplastic prodrug cyclophosphamide (leading to reduced antitumor efficacy) [84] or metabolize the antiretroviral efavirenz (leading to increased systemic toxicity) [85]; *CYP2A6*4* variants having slow nicotine metabolism [86,87] and an increased incidence of smoking behavior [88,89]; and *CYP1A2*1F* CC carriers with rheumatoid arthritis had 9.7-fold increase in toxicity with leflunomide when compared to carriers of the A allele [90]. These associations should be interpreted with caution, as they mostly represent small, single center genotype-phenotype association studies. Combination of variants like these in the pharmacokinetic pathway with variants in the pharmacodynamic pathway, similar to the warfarin and *CYP2C9/VKORC1* example, will likely lead to increased predictive power of the effect of variation in these minor metabolizing enzymes on clinical practice.

Other Phase I Enzymes—One of the earliest pharmacogenetic observations involved what is now considered one of the minor phase I enzymes. In the early 1950s, acute hemolysis was noted in a subset of mostly males treated with a new antimalarial agent, primaquine [91,92]. Subsequent studies in prisoners revealed patients that developed hemolysis when exposed to primaquine lacked the enzyme glucose-6-phosphate dehydrogenase in their erythrocytes [93]. The enzyme was linked to the long arm of the X chromosome and the molecular mechanism of this deficiency was elucidated in 1988 and found to be due to two polymorphisms in the gene leading to an unstable enzyme [94,95].

This enzymatic deficiency was also linked to a disease recognized since antiquity, favism. However, a different nucleotide substitution, C to T at position 563 in exon 6, was linked to the Mediterranean form of the disease [96].

Another important pharmacogenetic association involving a minor phase I enzyme was discovered as a result of investigations into toxic deaths from the fluoropyrimidine chemotherapy, 5-fluorouracil (5-FU). Patients who experienced severe or fatal toxicity from this medicine invariably had a decreased activity of dihydropyrimidine dehydrogenase (DPD) enzyme [97]. Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the pathway that catabolizes the pyrimidines such as uracil and thymine [98]. The frequency of low DPD enzyme activity is approximately 3-5% in the general population, but varies significantly among different ethnic populations [99-103]. *DYPD*, the gene encoding DPD, is subject to polymorphic variation with over 30 SNPs in the gene described to date, although very few of these SNPs have functional consequences [98]. Of particular interest is a splice site variant in intron 14 (IVS14+1G>A, *DYPD*2A*), which is found in 40-50% of patients with partial or complete DPD deficiency [104]. However, studies attempting to link severe fluoropyrimidine toxicity with variant *DYPD* genotypes have had varied success, with most studies having good specificity (82-100%) but poor sensitivity (6.3-83%) to detect risk of severe toxicity [105]. Functional testing of DPD activity by various techniques likely provide a more accurate assessment than *DYPD* genetic testing of a patient's risk of toxicity with fluoropyrimidine therapy. Current methods to functionally test DPD deficiency include incubation of patient peripheral blood mononuclear cells with radiolabeled 5-FU and measurement of metabolite formation by liquid chromotography [106], measurement of a plasma 5,6 dihydrouracil to uracil (UH_2/U) ratio prior to 5-FU treatment [107], and measurement of uracil catabolism via a uracil breath test [108]. A small single-center prospective trial of 5-FU dosing determined by DPD metabolic status measured with a plasma UH_2/U ratio revealed a significant reduction in adverse effects with no impact on therapeutic efficacy [109], a finding that suggests functional DPD testing and appropriate dose adjustments in deficient patients is feasible with the use of fluoropyrimidines.

The other minor phase I drug metabolizing enzymes: flavin monooxygenases, alcohol and aldehyde dehydrogenases, and the monoamine oxidases are also subject to polymorphic variation, some with functional consequences [110-113]. However, because these enzymes only have a minor role in the metabolism of prescribed drugs, polymorphisms in these enzymes will not be discussed further in this review.

THE PHASE II ENZYMES

The phase II enzymes are responsible for conjugating various molecules resulting in a more water soluble metabolite that can be excreted in the urine or stool. The phase II enzymes are also subject to phenotypic variation.

N-Acetyltransferases—Variations in acetylation leading to adverse drug events were some of the very first pharmacogenetic observations. In the 1950's, a new antituberculosis agent, isoniazid revolutionized the treatment of this deadly disease. However, a rare adverse event, peripheral neuritis, was noted in some patients treated with isoniazid [114]. Hughes and colleagues were able to demonstrate that patients with a slow conversion of isoniazid to acetylisoniazid were more susceptible to the development of peripheral neuritis [115]. Further investigations revealed that slow acetylation was a recessive trait [116] and that there was a wide range of slow acetylators between populations, with 10% of East Asians and up to 50% of Europeans exhibiting the phenotype [117]. Cloning of the cDNA responsible for isoniazid acetylation, *N*-acetyltransferase 2 (*NAT2*), was achieved 30 years

later [118] and several base substitutions creating variant alleles with absent enzyme activity made evident the molecular mechanism of slow acetylation [119,120].

Thiopurine Methyltransferase (*TPMT*)—To date, the only pharmacogenetic test involving a drug metabolizing enzyme that has gained widespread acceptance in clinical practice involves another phase II enzyme: thiopurine methyltransferase. The thiopurines, 6-mercaptopurine, 6-thioguanine azathioprine, were developed in the late 1940s and 1950s [121] and have been incorporated into the treatment of hematologic malignancies and autoimmune disorders as well as in the prevention of solid organ transplant rejection. The thiopurines are prodrugs that are converted by multiple enzymes into thioguanine nucleotides (TGN). TGNs are then incorporated into DNA. Inactivation of TGN occurs by two main mechanisms: oxidation by xanthine oxidase and methylation by TPMT. Xanthine oxidase activity is negligible in hematopoetic tissues, so these cells rely on TPMT for TGN inactivation.

Struck by the wide interpatient variability in both response and side effect profiles of patients treated with 6-mercaptopurine (6-MP), Weinshilboum and Sladek first described patients with undetectable erythrocyte TPMT activity [122]. Based on the population distribution of enzyme activity they identified that TPMT enzyme activity was inherited in a codominant fashion, and that 1 in every 300 patients lacked TPMT activity altogether [122]. Subsequent studies revealed that adverse events like drug induced neutropenia were directly correlated with the accumulation of the TGN, and that patients with absent erythrocyte TPMT activity had marked accumulation of these metabolites, and were much more prone to toxic side effects [123]. Conversely, patients with low TGN concentrations and high erythrocyte TPMT concentrations had an increased incidence of relapse of their leukemia when being treated with standard doses of 6-MP [123]. Localization and cloning of wild-type *TPMT* and 2 common alleles (*TPMT*2* and *TPMT*3A*), each leading to amino acid substitutions and absent enzyme activity, was achieved in 1996 [124,125]. The two variant alleles as well as *TPMT*3C account for 95% of intermediate or low enzyme activity cases [126]. Thiopurine dose modifications based on TPMT activity have been adopted widely in the treatment of autoimmune disease [127], and in the treatment of childhood acute lymphoblastic leukemia [128,129].

UDP Glucuronyltransferases (UGTs)—Glucuronidation represents a major pathway that enhances the elimination of many lipophilic xenobiotics and endobiotics to more water-soluble compounds. Over 35 different UGT gene products have been described from several different species. UGTs have been divided into two distinct subfamilies based on sequence identities, UGT1 and UGT2. In his classic paper reviewing early important pharmacogenetic associations, Motulsky mentioned the mild hyperbilirubinemia of Gilbert syndrome, caused by the inability to conjugate bilirubin, and hypothesized that variations in drug glucuronides may be from a similar mechanism [1]. In fact, these two phenomena were shown to be from deficiencies in UGT activity [130]. Cloning of the UGT variant responsible for Gilbert syndrome, *UGT1A1*28* – a TA insertion in the promoter region of the gene leading to decreased transcription, was achieved in 1996 [131]. This variant has also been linked to severe hematologic and gastrointestinal toxicities with the antineoplastic agent irinotecan, because of absent conjugation and therefore delayed excretion of a toxic metabolite (SN-38) [132]. Several *UGT1A1* genotypes were shown to be associated with the development of severe toxicity with irinotecan [133-135], and in 2005, the United States FDA updated the drug label to include a consideration of dose reduction in patients homozygous for the *UGT1A1*28* allele. Studies evaluating the impact of dose modification based on *UGT1A1* genotype on preventing toxicity are ongoing.

GENOMIC APPROACHES TO UNDERSTANDING GENETIC VARIATION AND DRUG RESPONSE

Most, but not all, of the examples of genotype-phenotype relationships that have resulted in an FDA label change are from candidate gene studies. These studies focus on variants within one or more genes thought to have the largest effect on metabolism, disposition or mechanism of action. The value of this approach is that it deals with a limited number of genes and variants that have been previously studied; but it is biased by our limited knowledge of the mechanism of action of drugs. Given these limitations, genome wide approaches to discover variants important in drug response and/or toxicity have emerged.

Genome wide techniques treat all interrogated variants as equal in their potential to impact the phenotype of interest. The benefit of this technique is that variants outside of those known to be involved in metabolism, disposition and/or response have the potential to emerge as important factors and may highlight new genes important in the biology of metabolism or response for a given drug. For example, prior work established that approximately 30% of the warfarin dose variance is explained by SNPs in the warfarin drug target *VKORC1* and another approximately 12% by the warfarinmetabolizing gene *CYP2C9* [136,137]. However, a later genome-wide association study enhanced detection of weaker effects, by conducting a multiple regression adjusting for known influences on warfarin dose (*VKORC1*, *CYP2C9*, age, gender) and identified a SNP that alters protein coding of the *CYP4F2* gene [138]. Regardless of the technologies used to investigate pharmacogenetic or genomic relationships, for clinical genotype-phenotype studies, patients should be treated uniformly and phenotypes of interest (toxicity, drug response, pharmacokinetic data) should be systematically evaluated. An ideal setting for these types of studies is within the context of large multi-institution clinical trials, where comprehensive response and toxicity data (phenotype data) are kept and can be associated with genetic or genomic data extracted from patients enrolled on the trial.

Although only 2% of the human genome is genes, there has been a strong interest in studying regulatory sequences and non-coding sequences. Intergenic, intron and other non-coding regions may harbor regulators of gene expression [139]. In addition, microRNAs, short sequences encoded throughout the genome, are capable of binding to complementary sequences of mRNA, usually resulting in post-translational gene silencing [140]. Based on sequence homology, several microRNAs are thought to regulate drug metabolizing enzymes, including miR-133 and miR-137 with *VKORC1* and miR-22 with *MTHFR* [141]. There will be even more genetic information in the form of rare SNPs from The 1000 Genomes Project, that will allow a better view of contributions to phenotypic variation [142]. Sequencing data output will be concomitant with the development of powerful tools in bioinformatics for analyzing and storing vast amounts of data that will enable continued growth in the field of personalized therapeutics.

CONCLUSIONS AND FUTURE DIRECTIONS

Common variation in the coding sequence and/or regulatory regions of genes encoding drug metabolizing enzymes has explained a great deal of interindividual variation in response and toxicity with medications. However, drug metabolism is only one aspect of drug-gene interaction, and common genetic variations in the sequence encoding drug transporters, drug receptors, target genes and other pharmacodynamic genes have also been shown to impact toxicity and response to treatment. Many formerly idiosyncratic (not predictable by drug concentration) adverse drug reactions like hypersensitivity reactions, liver injury and prolongation of the QT interval can now be at least partially explained by variation in genes outside of the metabolic or therapeutic pathway such as genes encoding for human leukocyte antigens and voltage gated ion channels [143-145]. The post-genome era and advances in

microarray technology have made scanning a patient's entire genome for associations with drug response and/or toxicity much more affordable and practical.

Recognition of the potential of pharmacogenomics in eventually being able to accurately predict toxicity and response has led to the widespread collection and banking of DNA for both ongoing prospective and future genotype-phenotype association studies. Because the inherited component of drug response for a given drug is polygenic in the vast majority of cases, development of techniques for elucidating the multiple genes involved and algorithms to consider multiple alleles are of considerable interest. Using well-defined phenotypes is key to making reproducible genotype-phenotype correlations; however this presents a challenge when performing clinical studies where there are a number of confounding variables. Well designed prospective pharmacogenetic and pharmacogenomic studies will undoubtedly increase our knowledge of genetic markers predictive of drug response and toxicity, and lead to FDA label changes, and most importantly, improved efficacy and safety of current medications.

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Acknowledgments

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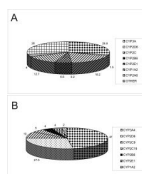
Fig. (1).
(**a**) Relative abundance of drug metabolizing enzymes in human liver microsomes, "other" includes non-P450 phase I enzymes and phase II enzymes [39]. Other includes minor phase I drug metabolizing enzymes as well as phase II enzymes. (**b**) Percentage of prescription drugs metabolized by each P450 enzyme [39].

Table 1

Overview of Common Genetic Variants in Phase I Drug Metabolising Enzymes

Gene	Important Variants	Variation	Consequence of Variation	Effect on Enzyme Activity	Selected Medication Substrates
CYP2D6	CYP2D6*3	2549 del A (rs4986774)	Frameshift mutation, premature stop	Absent activity	Amitriptyline, atomoxetine, carvedilol, chlorpheniramine, chlorpromazine, citalopram, clomipramine, clozapine, **codeine,** debrisoquine, desipramine, dextromethorphan, doxepin, flecainide, fluoxetine, fluvoxamine, gefitinib, haloperidol, imipramine, maprotiline, metoprolol, mexilet-ine, mianserin, morphine, nortriptyline, paroxetine, risperidone, **tamoxifen,** thioridazine, timolol, tolterodine, tramadol
	CYP2D6*4	1846G>A (rs3892097)	Splicing defect	Absent activity	
	CYP2D6*5	n/a	Whole gene deletion	Absent activity	
	CYP2D6*6	1707 del T (rs5030655)	Frameshift mutation	Absent activity	
	CYP2D6*9	2615_2617delAAAG (rs5030656)	Deletion of lys^{281}	Reduced activity	
	CYP2D6*10	100C>T (rs1065852)	$pro^{34}ser$	Reduced activity	
	CYP2D6*17	1023C>T (rs28371706)	$thr^{107}ile$	Reduced activity*	
	CYP2D6*29	3183G>A (rs59421388) and 4180G>C (rs61736512)	$val^{338}met$ and $ser^{486}thr$	Reduced activity	
	CYP2D6*41	2988G>A (rs28371725)	Splicing defect	Reduced activity	
	CYP2D6*UM	n/a	Additional functional copies (2–13) of gene	Increased activity	
CYP2C19	CYP2C19*2	681G>A (rs4244285)	Splicing defect, premature stop	Absent activity	lansoprazole, omeprazole, pantoprazole, rabeprazole, **phenytoin, phenobarbitone,** amitriptyline, carisoprodol, **clopidogrel,** citalopram, clomipramine, cyclophos-phamide, hexobarbital, imipramine, indomethacin, nelfi-navir, nilutamide, primidone, progesterone, proguanil, propranolol, teniposide, warfarin
	CYP2C19*3	636G>A (rs4986893)	Premature stop	Absent activity	
CYP2C9	CYP2C9*2	430C>T (rs1799853)	$arg^{144}cys$	Reduced activity	irbesartan, losartan, phenytoin, cyclophosphamide, tamoxifen, fluvastatin, celecoxib, diclofenac, ibuprofen, meloxicam, naproxen, glibenclamide, glimepiride, glipizide, tolbutamide, **warfarin**
	CYP2C9*3	1075A>C (rs1057910)	$ile^{359}leu$	Reduced activity	
CYP3A4	No clinically relevant variants described to date	N/A	N/A	N/A	clarithromycin, erythromycin, telithromycin, quinidine, alprazolam, diazepam, midazolam, triazolam, cyclosporine, tacrolimus, indinavir, nelfinavir, ritonavir, saquinavir, cisapride, astemizole, chlorpheniramine, terfenidine, amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil, atorvastatin, cerivastatin, lovastatin, simvastatin, estradiol, hydrocortisone, progesterone, testosterone, alfentanil, aprepitant, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, risperidone, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, ziprasidone, zolpidem

Gene	Important Variants	Variation	Consequence of Variation	Effect on Enzyme Activity	Selected Medication Substrates
CYP3A5	CYP3A5*3	6986A>G (rs776746)	Splicing defect, premature stop	Absent activity	Broad overlap with CYP3A4
	CYP3A5*6	14690G>A (rs10264272)	Splicing defect, removes exon 7	Absent activity	
	CYP3A5*7	27131-2insT (rs41303343)	Frameshift mutation	Absent activity	
CYP2B6	CYP2B6*6	516G>T (rs3745274)	his^{172}gln	Reduced activity	bupropion, **cyclophosphamide**, diazepam, **efavirenz**, ifosfamide, ketamine, methadone, MDMA, meperidine, mephenytoin, midazolam, nevirapine, nicotine, propofol, selegiline, tamoxifen
	CYP2B6*16	983T>C (rs28399499)	ile^{328}thr	Reduced activity	
	CYP2B6*18	1459C>T (rs3211371)	arg^{487}cys	Reduced activity	

Data compiled from http://www.pharmgkb.org and http://www.cypalleles.ki.se. Bold type indicates drug of particular interest to the corresponding gene.

*
while *CYP2D6*17* is generally considered to be a reduced function allele, evidence exists that this variant has normal activity towards risperidone [146].