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REVIEW

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects

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Interindividual differences in drug disposition are important causes for adverse drug reactions and lack of drug response. The majority of phase I and phase II drug-metabolizing enzymes (DMEs) are polymorphic and constitute essential factors for the outcome of drug therapy. Recently, both genome-wide association (GWA) studies with a focus on drug response, as well as more targeted studies of genes encoding DMEs have revealed in-depth information and provided additional information for variation in drug metabolism and drug response, resulting in increased knowledge that aids drug development and clinical practice. In addition, an increasing number of meta-analyses have been published based on several original and often conflicting pharmacogenetic studies. Here, we review data regarding the pharmacogenomics of DMEs, with particular emphasis on novelties. We conclude that recent studies have emphasized the importance of *CYP2C19* polymorphism for the effects of clopidogrel, whereas the *CYP2C9* polymorphism appears to have a role in anticoagulant treatment, although inferior to VKORC1. Furthermore, the analgesic and side effects of codeine in relation to *CYP2D6* polymorphism are supported and the influence of *CYP2D6* genotype on breast cancer recurrence during tamoxifen treatment appears relevant as based on three large studies. The influence of *CYP2D6* polymorphism on the effect of antidepressants in a clinical setting is yet without any firm evidence, and the relation between *CYP2D6* ultrarapid metabolizers and suicide behavior warrants further studies. There is evidence for the influence of *CYP3A5* polymorphism on tacrolimus dose, although the influence on response is less studied. Recent large GWA studies support a link between *CYP1A2* polymorphism and blood pressure as well as coffee consumption, and between *CYP2A6* polymorphism and cigarette consumption, which in turn appears to influence the lung cancer incidence. Regarding phase II enzyme polymorphism, the anticancer treatment with mercaptopurines and irinotecan is still considered important in relation to the polymorphism of *TPMT* and *UGT1A1*, respectively. There is a need for further clarification of the clinical importance and use of all these findings, but the recent research in the field that encompasses larger studies and a whole genome perspective, improves the possibilities be able to make firm and cost-effective recommendations for drug treatment in the future.

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INTRODUCTION

The majority of phase I and phase II drug-metabolizing enzymes (DMEs) are polymorphic. This polymorphism causes important interindividual differences in drug and metabolite exposure and can determine drug response as well as the risk for adverse drug reactions. In recent years, we have increased our understanding regarding the clinical importance of such variation and several databases containing pharmacogenetic information regarding DMEs are readily available (reviewed in Sim and Ingelman-Sundberg[1]).

Genetic polymorphism of *DMEs* encompasses gene copy number variation including gene amplification and deletion, small insertions and deletions, as well as single-nucleotide polymorphisms (SNPs). A recent study examining global and local differentiation SNP profiles in 283 *DME* as well as transporter genes across 62 worldwide ethnic groups indicated that there is a positive selection on variation in *DME* genes and that this genetic differentiation contributes to population heterogeneity in drug response.[2] The polymorphisms of *DME* genes are important determinants for drug response, and indeed the majority of pharmacogenomic drug labels refer to genes encoding phase I and phase II enzymes.[3] In addition, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) highlight such variation in specific guidelines in clinical pharmacology and for drug development (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243702.pdf). In the present review, our objective is to focus on novel aspects of *DME* pharmacogenetics, both in terms of identifying recent studies that have provided additional evidence to or strengthened already known *DME* associations, as well as studies on new associations or mechanisms of *DME* polymorphism influencing phenotype. Herein, we present an update on the impact of *DME* genotypes on the metabolism and outcome of drugs, as well as other exogenous and endogenous substances.

SNPS AFFECTING DME FUNCTION

Associations of SNPs to drug treatment outcome is continuously being discovered, with a recent focus on genome-wide association (GWA) studies being conducted in many different ethnic

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groups. Although several SNPs identified in GWA studies are linked with SNPs causing functional alterations, determining the function of SNPs without apparent linkage or proven effects is a more laborious task that represents a bottleneck between the numerous DME polymorphisms identified and their functional role and molecular mechanism of action. Although *DME* SNPs with confirmed effects have been reported for all gene regions such as in 5′- or 3′-untranslated regions, non-synonymous SNPs causing amino-acid substitutions constitute the major basis for assigning new alleles among the *Cytochrome P450 1-3 (CYP1-3)* gene families, with close to 400 different unique alleles characterized to date (www.cypalleles.ki.se). Examples of alleles carrying SNPs interfering with the splicing machinery include *CYP2D6*4*, *CYP2D6*41*, *CYP2C19*2*, *CYP2B6*6* and *CYP3A5*3* (reviewed in Sadee *et al.*[4]). Short nucleotide sequences directing the spliceosome to the correct exon–intron boundary have limited tolerance to mutations and hence can lead to aberrantly spliced transcripts and abolished protein function, such as for *CYP2C19*2*[5,6] and *CYB2B6*6*.[7–9] An example of *DME* polymorphism interfering with transcriptional regulation is the *UGT1A1*28* allele that harbors an extra promoter TA repeat leading to decreased gene expression,[10,11] whereas the *CYP2C19*17* (g.-806C>T) allele results in increased gene expression.[12] Increased transcription has also been reported for the g.-163C>A SNP variant in *CYP1A2*1F*, which can particularly enhance CYP1A2 inducibility (see for example, Djordjevic *et al.*[13] and Han *et al.*[14]). A more recent functional intronic SNP was identified for *CYP3A4* (g.15389C>T, rs35599367, *CYP3A4*22*), which was shown to reduce hepatic CYP3A4 mRNA levels potentially by disrupting the RNA elongation rate through changes in single-stranded DNA or RNA secondary structures.[15]

GWA STUDIES META-ANALYSES AND SPECIFIC STUDIES OF DME POLYMORPHISM OF CLINICAL OR ENDOGENOUS IMPORTANCE

Recent GWA studies, and meta-analyses, providing weighted measures based on several original studies, have significantly improved our knowledge regarding genetic variation in *DME* genes that cause alterations in drug disposition. GWA data have, in particular, provided substantial support to previous findings, indicating the importance of *DME* variants in drug response (for example warfarin and *CYP2C9*, clopidogrel and *CYP2C19*), as well as providing evidence for other levels of associations, such as that of genetic variation in the aryl hydrocarbon receptor (*AHR*, a known regulator of CYP1A2 expression) and *CYP1A2* (for which caffeine is used as a probe drug) with caffeine intake. In addition, GWA studies have established the relative role of the *CYP2A6* locus in smoking behavior. Interpretation of GWA data, however, also has some associated uncertainties. Substantial variation between different GWA studies with respect to SNP coverage, population size studied and integration of replication cohorts, has sometimes made it difficult to cross compare and validate the various result outcomes and conclusions derived. Furthermore, deep sequencing with a higher coverage of genetic variation than GWA studies may prove more successful in identifying novel pharmacogenetic associations of DMEs. There is a GWA study database available (from National Human Genome Research Institute (http://www.genome.gov/gwastudies/), however, this database does neither record the population sizes with high accuracy, nor does it report whether the genome-wide significance stated for a specific gene is related to exploratory analyses, replication analyses (of sometimes non-significant results in the exploratory analysis), or whether significance was obtained after adjusting for subject characteristics or even other genetic variants known to influence the outcome.

As for meta-analyses, they provide a more analytical perspective on genotype–phenotype relationships by combining multiple studies that evaluate specific associations (for example clopidogrel and *CYP2C19*, tamoxifen and *CYP2D6*) and thus offer a more comprehensive deduction than individual studies.

In the proceeding sections we review GWA studies, recent meta-analyses as well as relevant specific DME studies carried out in the field of DMEs and their influence on drugs and endogenous phenotypes (the strongest findings are summarized in Table 1 and Figure 1). Furthermore, the set-up and outcome of recent GWA studies showing DME associations have been summarized in Table 2.

PHASE I ENZYMES

CYP1A2, caffeine and blood pressure

Caffeine has long been known as one of the substrates and inducers of CYP1A2. In 2011, three independent GWA studies

Table 1. Drugs affected by DME polymorphism

Drug	*Clinical use*	*Impacting DME alleles*	*Literature support of DME biomarker*	*Impact of DME biomarker on PK*	*Impact of DME biomarker on clinical parameter*	*Type of clinical parameter affected*
Warfarin	Cardiovascular disorders	*CYP2C9*2* and **3*	Extensive	High	Modest	Bleeding
Clopidogrel	Cardiovascular disorders	*CYP2C19*2, *3, *17*	Extensive	High	Modest	Stent thrombosis and bleeding
Tamoxifen	Breast cancer	*CYP2D6 (various)*	Relatively good	High	Modest	Breast cancer recurrence
Tacrolimus	Organ transplantation	*CYP3A5*3*	Relatively good	Relatively strong	Small	Graft rejection
Antidepressants	Depression	*CYP2D6 (various)*	Insufficient number of studies	High	Unknown	Non-response
Escitalopram	Depression	*CYP2C19*17*	Insufficient number of studies	High	Unknown	Non-response
NSAIDs	Pain relief	*CYP2C9*2* and **3*	Insufficient number of studies	Modest	Unknown	GI bleeding
Irinotecan	Colorectal cancer	*UGT1A1*28*	Good	High	Modest	Myelotoxicity
6-MP and AZA	Leukemia and chronic inflammation	*TPMT*2, TPMT*3A* and *TPMT*3C*	Good	High	Modest	Myelotoxicity
Codeine	Pain relief	*CYP2D6 (various)*	Relatively good	High	Limited	Response or CNS depression

Abbreviations: AZA, azathioprine; CNS, central nervous system; DME, drug-metabolizing enzyme; GI, gastrointestinal; 6-MP, 6-mercaptopurine; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic.

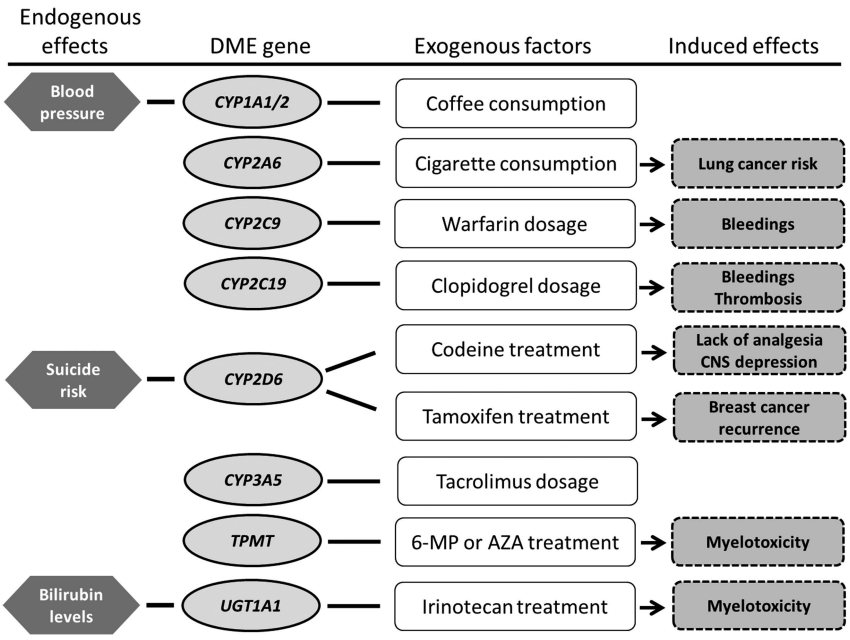

Figure 1. Summary of the major effects of *DME* polymorphism on outcome of drug and exogenous exposure, as well as endogenous phenotypes. 6-MP, 6-mercaptopurine; AZA, azathioprine.

amounting to $>72\,000$ subjects in total, found an association between *CYP1A2* variation and the habitual consumption of coffee (see Table 2). In a genome-wide meta-analysis of 47 341 subjects, Cornelis *et al.*[16] first presented an association between the behavioral caffeine intake trait and variations in both the *CYP1A1-1A2* bidirectional promoter as well as a locus upstream the *AHR* that regulates the expression of *CYP1A* genes. These findings were later corroborated in another GW meta-analysis by Sulem *et al.*,[17] whereas Amin *et al.*[18] identified the *CYP1A* locus but not that of *AHR*. The effect of each individual *CYP1A2* and *AHR* allele has been estimated to about 0.2 coffee cups per day.[17] However, the identified polymorphisms at the two loci were together found to explain $<1\%$ of the caffeine intake variation,[16] suggesting other factors with potentially greater importance are also involved. Interestingly, these two loci are hitherto the only ones identified to have an effect on caffeine intake, and thus the adenosine receptors, on which caffeine acts, have not been picked up by GWA studies. The *CYP1A* locus has also been associated with blood pressure in two large GWA studies[19,20] (see Table 2). Furthermore, carriage of the -163C allele (that is *CYP1A2*1A*), was significantly associated with an increased risk of developing stage 2 hypertension compared with homozygotes for -163A (that is *CYP1A2*1F/*1F*) in a study of 553 stage 1 hypertension patients; however, only among the subgroup of coffee consumers.[21] It is important to note that in this paper, the *CYP1A2*1A* allele was specified as *CYP1A2*1F* and vice versa (although correctly described in this review, see http://www.cypalleles.ki.se). Further support was published recently by Guessous *et al.*,[22] who found a relationship of the *CYP1A2*1F* allele with increased caffeine intake and reduced risk of hypertension among non-smokers, with additional independent associations for two other SNPs in the same locus. The authors hypothesize that the increased caffeine intake, which is caused by *CYP1A2* polymorphism, accounts for the genetic impact of *CYP1A2* on blood pressure, and that CYP1A2 induction by smoking blunts these genetic effects.[22] In summary, GWA study data and specific association studies do support a role of CYP1A2 in the regulation of blood pressure, although further investigations will likely shed more light on the mechanistic aspects.

CYP2A6 and smoking

CYP2A6 is the main enzyme involved in the metabolism of nicotine, and the influence of CYP2A6 polymorphism on smoking behavior has been extensively studied (see Gold and Lerman[23]). A recent GWA study by Thorgeirsson *et al.*[24] found that SNP variation in both *CYP2A6* (19q3) and nicotinic acetylcholine receptors (*nAchR*, 15q25) containing loci significantly affected cigarette consumption (European Network for Genetic and Genomic Epidemiology Consortium, $n=31\,266$). Furthermore, the highly frequent *CYP2A6*2* allele (rs1801272, allele frequency up to 10%) that gives rise to abolished CYP2A6 enzyme activity was found associated with a significantly lower number of cigarettes smoked per day (reduction of 0.68 cigarettes per day and *CYP2A6*2* allele) ($n=66\,380$, $P=1.1\times10^{-4}$), which was close to the effect observed for *nAchR* variation (0.80 cigarettes per day and allele, $n=76\,972$, $P=2.4\times10^{-69}$).[24] On the contrary, genome-wide significance for cigarette consumption was mainly found for the nicotinic receptor gene cluster and no apparent effect of *CYP2A6* was observed in an analysis of 38 181 smokers (Tobacco and Genetics Consortium), although a follow-up analysis of 15 selected loci in 73 853 subjects identified a locus 40 kb downstream of *CYP2A6* that was estimated to cause a 0.33 cigarette per day difference per allele.[25] A smaller study ($n=3441$)[26] found only nominally significant associations of *CYP2A6* with cigarette consumption (0.27 cigarettes per day and allele for *CYP2A6*2*, $P=2.88\times10^{-5}$). A recent small and preliminary study examining functional magnetic resonance imaging of 31 subjects matched for cigarette consumption indicated that smokers with a reduced CYP2A6 phenotype or genotype ($n=13$–16) respond less to smoking cues in several regions of the brain compared with extensive metabolizers (EMs, $n=15$–18).[27] However, this finding has to be reproduced in a larger set of individuals.

Thorgeirsson *et al.*[24] also performed a genotype-based analysis of the *CYP2A6* rs4105144 genotype, which exists in linkage disequilibrium with the defective *CYP2A6*2* variant, in approximately 2000 lung cancer cases and 40 000 controls, where a small increased risk of lung cancer development was

Table 2. Genome-wide association studies with respect to drug metabolizing enzymes

Parameter studied	*Significant gene or gene-containing locus*	*Exploration cohort*	*Replication cohort*	*Number of SNPs analyzed*	*GW significance treshold (P <)*	*Association P-value*	*Comments*	*Reference*
Endogenous associations								
Bilirubin levels	UGT1A1	619 healthy African Americans	—	808 465	5.0×10^{-8}	2.0×10^{-22}	—	117
Bilirubin levels	UGT1A1	4300 healthy Sardinians	2692 healthy Sardinians	362 129	1.3×10^{-7}	6.2×10^{-62}	—	115
Bilirubin levels	UGT1A1	9464 healthy Caucasians	—	~2.5 m genotyped and imputed	5.0×10^{-8}	5.0×10^{-324}	Meta-analytical *P*-value	116
Blood pressure	CYP1A	69 395 healthy subjects	Up to 133 661 healthy subjects	~2.5 m genotyped and imputed	2.5×10^{-8}	2.7×10^{-26}	—	20
Blood pressure	CYP1A	134 258 healthy subjects	—	~2.5 m genotyped and imputed	5.0×10^{-8}	1.0×10^{-23}	Meta-analytical *P*-value (borderline significant in primary GW cohort, $n = 34\,126$, $P = 6.0 \times 10^{-8}$)	19
Drug and exogenous associations								
Acenocoumarol dose	CYP4F2	1451 Caucasian patients	287 Caucasian patients	~550 000	5×10^{-8}	2.0×10^{-8}	GWA analyses performed on data adjusted for *VKORC1* and *CYP2C9* genotype, age, gender, BMI and target INR	35
Acenocoumarol dose	CYP2C9	1451 Caucasian patients	287 Caucasian patients	550 000	5×10^{-8}	3.3×10^{-24}	GWA analyses performed on data adjusted for age, gender, BMI and target INR	35
Caffeine consumption	CYP1A	18 176 healthy Caucasians	7929 healthy Caucasians	~2.6 m genotyped and imputed	5.0×10^{-8}	2.4×10^{-8}	—	18
Caffeine consumption	CYP1A	47 341 healthy Europeans	—	433 781	1.0×10^{-6}	5.2×10^{-14}	Meta-analytical *P*-value	16
Caffeine consumption	CYP1A	6611 healthy Caucasians	4050 healthy Caucasians	~2.5 m genotyped and imputed	5.0×10^{-8}	1.8×10^{-10}	Meta-analytical *P*-value	17
Cigarette consumption	CYP2A6	73 853 healthy Europeans	—	~2.5 m genotyped and imputed	5.0×10^{-8}	1.0×10^{-8}	Meta-analytical significance only in specific analysis of 15 selected loci	25
Cigarette consumption	CYP2A6	31 266 healthy Europeans	83 317 healthy Europeans	~2.5 m genotyped and imputed	5.0×10^{-8}	1.2×10^{-9}	Meta-analytical *P*-value	24
Clopidogrel antiplatelet effect	CYP2C19	429 healthy Amish subjects	227 mixed-ethnicity patients	400 230	1.0×10^{-7}	1.5×10^{-13}	—	43
Warfarin dose	CYP2C9	807 low-dose, 701 high-dose Japanese patients	444 Japanese patients	485 227	1.0×10^{-7}	3.8×10^{-7}	Only close to significant	34
Warfarin dose	CYP2C9	181 European patients	374 European patients	538 629	1.0×10^{-7}	9.7×10^{-5}	Significant only in the combined exploration and replication cohorts ($P = 6.2 \times 10^{-12}$)	32
Warfarin dose	CYP2C9	1053 Swedish patients	588 Swedish patients	325 997	1.5×10^{-7}	3.1×10^{-31}	—	33
Warfarin dose	CYP4F2	1053 Swedish patients	588 Swedish patients	325 997	1.5×10^{-7}	8.3×10^{-10}	Significant after adjusting for *VKORC1* and *CYP2C9* genotype	33

Abbreviations: BMI, body mass index; GWA, genome-wide association; INR, international normalized ratio; SNP, single-nucleotide polymorphism.

found for the major *CYP2A6*1* allele (odds ratio, OR = 1.09, $P = 0.04$). Similarly, a reduced risk of lung cancer has been found for carriers of defective *CYP2A6* alleles (for example *CYP2A6*2* and **4*) in Caucasian and Asian populations, and an enhanced *CYP2A6* genotype effect was seen among smokers and for smoking-related lung cancer types (squamous cell lung carcinoma).[28–31] Thus, the link between *CYP2A6* genotype and smoking has been emphasized recently, particularly with support from large GWA studies.

CYP2C9, CYP4F2 and warfarin

Coumarin-related drugs, used as anticoagulants for a variety of cardiovascular disease, are primarily metabolized by CYP2C9. They have a very narrow therapeutic index and a significant associated risk of bleeding and embolism. GWA studies on warfarin maintenance dosing have been performed in three different populations of Caucasians and Asians using univariate analyses.[32–34] In all studies, *VKORC1* emerged as the main contributor to determining the response to warfarin, whereas *CYP2C9* showed a smaller but yet significant contribution in Swedish subjects ($n = 1053$),[33] a GW significant trend in Japanese subjects ($n = 1508$),[34] but being only moderately significant in a smaller cohort of European ancestry ($n = 181$).[32] After adjusting for *VKORC1* and *CYP2C9* genotype, age and gender by multiple regression analysis, *CYP4F2* also reached GW significance in Swedes,[33] whereas multiple regression did not lead to GW significance for *CYP4F2* in Japanese subjects.[34] *CYP2C9* has also been found significant at a genome-wide level for acenocoumarol dosing in a study of 1450 subjects analyzed by a regression model adjusted for age, gender, BMI and the prothrombin international normalized ratio (INR) target measurement.[35] Further adjusting for *CYP2C9* and *VKORC1* genotype identified *CYP4F2* as GW significant in affecting acenocoumarol dosing.[35] In support for the clinical relevance of genetic variants on warfarin dose variation, Epstein *et al.*[36] found in a prospective study that the hospitalization rate for bleeding or thromboembolism caused by warfarin during the initial 6-month period is up to 43% lower in patients genotyped for *VKORC1* and *CYP2C9* polymorphisms to direct drug dosage ($n = 896$) when compared with an age- and sex-matched non-genotyped control group from the same prescription benefit regime ($n = 2688$). Furthermore, a study of 477 patients with *VKORC1* and *CYP2C9* genotype-guided warfarin dosing revealed that the guided method decreased the percentage of patients being out of range in INR and increased the time spent in therapeutic range to up to 3 months when compared with the 1866 patients treated in parallel by a standard scheme.[37] Although both *VKORC1* and *CYP2C9* have been recently shown clinically relevant in warfarin guidance, further analyses of the pharmacological relevance is still necessary, especially for the specific impact of *CYP2C9*. At present, it appears that the genes together are able to predict about 35% of the variation in dosing; however, with *VKORC1* being much more important than *CYP2C9*. Currently, drug regulatory agencies do not require genotyping before warfarin initiation; however, the warfarin drug label in the USA (Coumadin, FDA) presents three dosing subgroups based on the combined *VKORC1* and *CYP2C9* genotypes that should be considered if the patients' genotype is known.

CYP3A4, statins and immunosuppressants

As mentioned, *CYP3A4*22* (rs35599367), with an allele frequency of only a few percent, carries a mutation in intron 6 that causes reduced mRNA expression.[15] Clinically, the *CYP3A4*22* allele has been shown to influence the pharmacokinetics of cholesterol-lowering statin drugs[15,38] as well as the immunosuppressants tacrolimus[39,40] and cyclosporine.[40] However, a follow-up study examining cyclosporine pharmacokinetics showed that the cyclosporine dose, blood concentration, rejection rate and delayed graft function were similar between cyclosporine-treated renal graft patients carrying the *CYP3A4*22* allele (heterozygous, $n = 11$) and non-carriers ($n = 161$).[41] Still, creatinine clearance was significantly reduced 3 months post transplant in *CYP3A4*1/*22* patients as compared with those homozygous for the wild-type allele.[41] In addition, when including co-variables in the analysis, the risk of delayed graft function was shown to be increased in *CYP3A4*1/*22* patients, as 5 out of the 11 *CYP3A4*22* carriers showed delayed graft function (45%) as compared with 26% in the total sample ($n = 39$).[41] The mechanism behind the potential increased risk for kidney impairment in transplantation patients carrying the *CYP3A4*22* allele is presently unknown, and additional studies need to conform this finding.

CYP2C19 and clopidogrel

The antiplatelet agent Clopidogrel (Plavix) is extensively used worldwide for the prevention of ischemic events particularly in patients with coronary syndromes, percutaneous coronary intervention (PCI) and myocardial infarction. CYP2C19 has a major role in activating clopidogrel, and Hulot *et al.*[42] were the first to demonstrate that the locus containing the *CYP2C19* gene influenced its antiplatelet response. A proceeding GWA study on clopidogrel performed by Shuldiner *et al.*[43] found that only the *CYP2C19* polymorphism showed GW significance with respect to drug levels in healthy subjects, and the same study also showed that the defective *CYP2C19*2* allele was associated with increased risk of cardiovascular events in patients. The clinical importance of *CYP2C19* genotype on clopidogrel treatment has been extensively studied in recent years and a number of different meta-analyses, integrating between 7 and 32 studies with 8000–42 000 subjects per analysis, have been published.[44–52] Most meta-analyses have addressed the effect of the defective *CYP2C19* alleles (here called *CYP2C19-def* and mainly composed of *CYP2C19*2* alleles) on clopidogrel treatment response. Some studies have also found that rapid CYP2C19 metabolism caused by the *CYP2C19*17* allele is associated with reduced risk of cardiovascular events as well as increased risk of bleedings;[45,47,48,53] however, contradictory results have also been reported.[46] The most recent and largest meta-analysis was published by Holmes *et al.*;[44] it encompassed 32 studies and 42 016 patients and showed that the risk of bleeding was reduced in carriers of *CYP2C19-def* alleles (relative risk, RR = 0.84; 95% confidence interval (CI), 0.75–0.94), with the risk of cardiovascular events also moderately increased (RR = 1.18; 95% CI, 1.09–1.28), the significance of which however was lost when including only larger studies encompassing >200 events. Although Holmes *et al.*[44] tend to smooth over the influences by *CYP2C19* genotype on clopidogrel response, specific analyses of cardiovascular events such as myocardial infarction or stent thrombosis were all below 200 events per study where, for medium size studies (100–199 events per study), an increased risk for myocardial infarction as well as stent thrombosis was evident (RR = 1.29, 95% CI, 1.06–1.58, and RR = 1.54, 95% CI, 1.26–1.88, respectively). Strong criticism has been raised against the performance and interpretation of the meta-analysis, as studies that contained patients without a clear benefit of clopidogrel were included and emphasized, whereas the number of patients with PCI, in which clopidogrel has the highest indication and benefit, was low.[54–56] Overall, the many meta-analyses have indicated the strongest effect of *CYP2C19-def* alleles on stent thrombosis, whereas *CYP2C19*17* seems to have a similar effect on bleedings as well as cardiovascular events, although seemingly smaller in magnitude compared with *CYP2C19-def*.

Combined clinical variables such as age and diabetes have been suggested as more important in determining clopidogrel effects than *CYP2C19-def* genotypes.[57] Interestingly, however, data available in Bouman *et al.*[57] indicate that the defective *CYP2C19*2* allele significantly impacts on platelet reactivity in response to

clopidogrel more than any separate clinical variable. This is corroborated by Mega *et al.*[58] who showed that increasing the dose of clopidogrel from 75 to 225 mg in *CYP2C19-def* heterozygote individuals leads to platelet reactivity measures similar to those of EMs (*CYP2C19*1/*1*), whereas however, sufficient inhibition of platelet reactivity could not be obtained in homozygous *CYP2C19-def* subjects with doses up to 300 mg. Furthermore, in a group of patients undergoing PCI, 91 subjects were subjected to a rapid genotyping scheme whereas 96 subjects went through standard clopidogrel treatment (75 mg per day).[59] In the genotyping group, *CYP2C19*2* carriers were allocated to prasugrel, with remaining subjects allocated to standard clopidogrel treatment.[59] After 1 week of treatment, all 23 *CYP2C19*2* carriers (100%) on prasugrel had sufficient inhibition of platelet reactivity, compared with 70% of *CYP2C19*2* carriers (16 of 23) on standard treatment ($P = 0.009$).[59] In addition, platelet inhibition after 1 week of treatment among the *CYP2C19*2* carriers was 73% in the genotype-guided group (prasugrel) but only 27% in the standard treatment group (clopidogrel; $P < 0.0001$),[59] thus supporting a genotype-based treatment scheme for patients undergoing PCI.

Bouman *et al.*[60] also found paraoxonase-1 to be a crucial enzyme in clopidogrel activation; however, not a single of many published studies have been able to confirm these findings, neither in gene-specific approaches (see for example, Sibbing *et al.*,[61] Trenk *et al.*[62]) nor in GWA studies.[43]

In summary, despite the large number of studies published on this topic, guiding clopidogrel dosing based on *CYP2C19* genotype is still a matter of debate. The significance of the *CYP2C19* polymorphism is definitely stronger when one considers myocardial infarction and especially stent thrombosis. Whether the black box warning introduced by the FDA 2 years ago is relevant or of lower importance than initially thought is still being discussed. In addition, as the efficacy of the newer platelet aggregation inhibitors prasugrel and ticagrelor do not require activation of polymorphic enzymes, this issue might be less important in the future. On the basis of the initial prospective studies, however, it appears that genotype-guided treatment schemes is beneficiary for PCI patients in selecting the right antiplatelet regimen.

CYP2C19, CYP2D6 and tamoxifen treatment of breast cancer

Adjuvant antiestrogenic tamoxifen treatment has long been a standard for estrogen receptor-positive breast cancer. Conversion of tamoxifen into the high-affinity estrogen receptor antagonist endoxifen requires metabolism, which to a large extent is carried out by CYP2D6. There is a general consensus that the formation of endoxifen is highly linked to CYP2D6 polymorphism,[63–65] whereas the effect of *CYP2D6* genotype on the pharmacodynamic response to tamoxifen has not been clearly defined.[65] The majority of clinical studies investigating *CYP2D6* genotype in relation to tamoxifen response have included small patients cohorts and, in addition, have been limited in terms of coverage of *CYP2D6* alleles. Two meta-analyses have been published in the field,[66,67] but both analyses were limited to the *CYP2D6*4* and **10* alleles as well as covering mostly small studies, which resulted in a small to non-existent effect of *CYP2D6* genotype on tamoxifen outcome. High *CYP2D6* allele coverage is an important factor in accurate determination of CYP2D6 effects, as exemplified by a power increase from 8 to 63% and a concomitant decrease in the *P*-value of recurrence hazard ratio analyses by increasing the allele coverage from *CYP2D6*4* only to 33 alleles.[68,69] Recently, larger studies on *CYP2D6* genotype and tamoxifen response have been published, where six studies qualify for a $\sim$500 participant selection of invasive non-metastatic breast cancer in either postmenopausal women or a mix of pre- and postmenopausal women where postmenopausal women were always composing at least 75%.[68–73] Median follow-up was at least 5 years for all studies and the treatment regimens were to a major extent non-chemotherapy-based (75–100%). Furthermore, a minimum of six *CYP2D6* alleles were genotyped in all studies and breast cancer recurrence was the main outcome parameter in all but one study.[73] Of utmost importance, however, is the serious criticism raised against two of the five studies on breast cancer recurrence that did not find any relationship between *CYP2D6* genotype and tamoxifen response.[71,72] This is apparently due to a lack of Hardy–Weinberg equilibrium, which was caused by genotyping analyses of tumor instead of germline DNA samples, as tumoral chromosomal rearrangements can occur in the region containing *CYP2D6*.[74] The remaining three large studies on breast cancer recurrence all found a significant effect of *CYP2D6* polymorphism on tamoxifen treatment response (Table 3). Taking these large recurrence studies together, one might conclude an overall odds ratio of between 2 and 3 for poor metabolizers. However, it must be emphasized that two of the three studies have used both tumor and lymphocyte derived DNA for genotyping analyses.[69,70]

Recently, a GWA study presented associations of the *C10orf11* gene with recurrence-free survival in 240 tamoxifen-treated breast cancer patients.[75] Although *CYP2D6* was not identified

Table 3. Association of CYP2D6 genotype with tamoxifen (20 mg for 5 years) response in larger (around 500 patients or more) studies of invasive, non-metastatic breast cancer

Cohort	*n*	*Chemo*	*Menopause*	*Follow-up years (median or mean)*	*CYP2D6 genotype coverage*	*CYP2D6 GCN covered*	*Genotype-predicted phenotypes analyzed*	*Results*	*Reference*
ATAC; Germany and USA	1 325	No	96% Post	6	*3, *4, *5(del),*10, *41, *X2(dupl)	Yes	IM ($n = 637$) or PM ($n = 79$) vs EM ($n = 609$)	IM vs EM: HR = 1.40 (95% CI, 1.04–1.90) for time to recurrence PM vs EM: HR = 1.90 (95% CI, 1.10–3.28) for time to recurrence	70
ATAC; Germany	492	No	97% Post	5	AmpliChip CYP450 (33 alleles)	Yes	PM ($n = 41$) vs EM ($n = 183$)	PM vs EM: HR = 2.87 (95% CI, 1.35–6.10) for recurrence PM vs EM: HR = 2.77 (95% CI, 1.35–6.10) for time to recurrence *(Results dependent on CYP2D6 genotype coverage)*	68
UK	618	18%	75% Post	4–10	*2, *3, *4, *5(del), *6, *7, *9, *10, *35, *41, *X2(dupl)	Yes	Decr. ($n = 225$) vs EM ($n = 126$)	Decr. vs EM: HR = 1.96 (95% CI, 1.05–3.66) for recurrence in postmenopausal/ No-chemo subgroup ($n = 351$) *(Results dependent on CYP2D6 genotype coverage)*	69

Abbreviations: CI, confidence interval; EM, extensive metabolizer; HR, hazard ratio; IM, intermediate metabolizer; PM, poor metabolizer.

at the genome-wide level, it was shown that allelic variation in the *C10orf11* gene together with variation in the two candidate genes *CYP2D6* and *ABCC2* had a cumulative effect on tamoxifen outcome with respect to the total number of risk alleles among all three genes.[75] More studies are needed, in particular with respect to the relationship between *CYP2D6* polymorphism and survival.

Polymorphism of *CYP2C19* has also been implicated in the response to tamoxifen recently, however, the data thus far have been contradictive.[76–78]

CYP2B6 and non-nucleoside reverse transcriptase inhibitors (NNRTIs)

CYP2B6 metabolizes the two NNRTI's nevirapine and efavirenz that are used for the treatment of HIV infection (cf[79]). Nevirapine levels and clinical outcome has been associated with the *CYP2B6* c.516G > T variant that causes a Q172H amino acid substitution commonly present in several different *CYP2B6* alleles (see www.cypalleles.ki.se/cyp2b6.htm). In a study of 126 children, homozygosity for the 516T allele was associated with reduced nevirapine clearance and an enhanced increase in CD4 + T cells both at 12 and 24 weeks of treatment.[80] Furthermore, in analyses of 175 subjects with cutaneous adverse events and 587 controls, the *CYP2B6* 516TT genotype appeared to modify the risk for nevirapine-induced and HLA-related (*HLA-Cw*04*) cutaneous adverse events, increasing the odds ratio from 2.4 (95% CI, 1.4–4.1) to 6.3 (95% CI, 2.5–15.7) when compared with the wild-type 516GG genotype.[81] An enhanced frequency of early efavirenz treatment discontinuation (OR = 2.6, 95% CI, 1.3–5.2) has also been associated with the *CYP2B6* 516TT genotype in a study of 373 efavirenz-treated patients,[82] which however was not found in a smaller study of 105 subjects.[83] In addition to NNRTI drug response, the *CYP2B6* genotype at position 516 and 983 corresponding to *CYP2B6*16* and **18* was shown to influence central nervous system (CNS) adverse events in Whites,[84] thus supporting previously observed CNS-related effects (mood disorder, sleep disorder, fatigue).[85,86] In conclusion, the *CYP2B6* polymorphism could be of significance for outcome of NNRTI treatment.

CYP3A5 and tacrolimus

Therapeutic drug monitoring is highly recommended for transplant patients receiving the immunosuppressive drug tacrolimus, as tacrolimus is subject to pharmacokinetic inter-patient variability and since its therapeutic window is small. Kidney transplantation is the most common indication for tacrolimus, and the drug is mainly metabolized by CYP3A enzymes where the common defective *CYP3A5*3* allele is the most significant genetic determinant. In white populations, the frequency of carriers of the wild-type *CYP3A5*1* allele (carriers are commonly referred to as CYP3A5 'expressors') is only about 15%, whereas it is up to 50% and 90% in Asians and Blacks, respectively (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=776746). As reviewed by Barry and Levine,[87] the weighted mean oral clearance of five studies is almost 50% lower (range 26–65%) in *CYP3A5*3* homozygotes (CYP3A5 'non-expressors') compared with *CYP3A5*1* carriers. A recent meta-analysis by Tang *et al.*[88] addressed dose requirements and rejection rates in 18 studies of renal transplant patients ($n = 1443$) and five studies of liver transplants ($n = 336$), and a clear effect of *CYP3A5* genotype was claimed on tacrolimus dose at all treatment follow-up occasions (2 weeks to 12 months). However, an effect on rejection rates was concluded only after the first month of treatment, which is mirrored by the most prominent effect of *CYP3A5* genotype on tacrolimus dose at this time point.[88] Thus, *CYP3A5* genotyping could be a useful tool to guide tacrolimus initiation doses in the prevention of early graft rejection.

CYP2C19, CYP2D6 and antidepressant treatment

CYP2D6 is involved in the metabolism of many antidepressants, and poor response of antidepressants has been associated with SNP polymorphism as well as the ultrarapid metabolizer (UM) phenotype caused by gene amplification,[89–93] although negative findings have also been observed for *CYP2D6* polymorphism.[94–96] On the basis of the variable types of antidepressants, differences in outcomes measured and a relatively low sample size in most studies, no clear conclusion can at present be drawn on the impact of *CYP2D6* genotype on response to antidepressants. As for duplicated *CYP2D6* genes, suicide rates and suicide behavior has been shown to be enhanced in UMs.[97–100] An enhanced suicide effect could be due to increased antidepressant elimination and thus poor response, or to an endogenous effect not related to antidepressant treatment (see below).

CYP2C19 effectively metabolizes escitalopram and the serum levels vary according to *CYP2C19* genotype.[101,102] The defective *CYP2C19*2* allele has also been associated with depressive symptoms in older healthy subjects from the Swedish Twin Registry suggesting endogenous effects,[103] and the rapid *CYP2C19*17* allele has shown to reduce the remission rate within the group of subjects that tolerated escitalopram in the STAR*D study (OR = 0.80, 95% CI, 0.63–1.00).[104] Further studies are needed before conclusions can be drawn with respect to antidepressant response as well as endogenous functions for CYP2C19 and CYP2D6.

CYP2D6 and codeine

CYP2D6 activates codeine into the analgesic substance morphine. Although no analgesic effect is obtained in CYP2D6 poor metabolizers, UMs are at risk of excessive morphine levels causing, for example, sedation and respiratory depression both in adults and in infants of CYP2D6 UM breast-feeding mothers (see for example Sim and Ingelman-Sundberg[1] and Supplements in Crews *et al.*[105]). Sistonen *et al.*[106] retrospectively addressed infant CNS depression (sleepiness and lethargy) among 26 infant cases and 85 infant controls being breast-fed by mothers taking codeine. Although the main risk factor for infant CNS depression was maternal CNS depression (58% in infant cases vs 7% in infant controls, $P = 1.5 \times 10^{-7}$), the maternal *CYP2D6* genotype increased the risk of infant CNS depression (OR = 17, $P = 0.043$).[106] FDA has included codeine drug label information on increased bioactivation in CYP2D6 UMs and the preference to choose lower doses for the shortest period of time in breast-feeding mothers as well as in the general population, to avoid overdose symptoms such as sleepiness, confusion or shallow breathing.

CYP2D6 and endogenous brain functions

CYP2D6 polymorphism has been suggested to influence personality traits, and allusions to an association with schizophrenia and Parkinson's disease has been claimed (see Dorado *et al.*[107]). Recently, a number of studies have found a relationship between *CYP2D6* genotype and suicidal behavior that is manifested in an overrepresentation of alleles with more than two *CYP2D6* gene copies (UMs) in suicidal subjects.[97–100] Furthermore, this risk was suggested to lie solely or partly in a more severe type of suicidal behavior among UMs as found by Penas–Lledo *et al.*,[97] thus potentially leading to a higher rate of deaths resulting from suicide attempts. It is known that CYP2D6 is able to metabolize CNS active substances and that CYP2D6 is expressed in the brain (see[1]). Recently, Kirchheiner *et al.*[108] were able to show that brain blood perfusion levels were affected by *CYP2D6* genotype. Poor metabolizers were found to have a 15% higher thalamic blood perfusion level than EMs at rest ($P < 0.05$),[108] although no *CYP2D6* genotype difference could be observed in terms of thalamus activation.[109] Instead, a working memory task was found to

display *CYP2D6* genotypic differences in the activation level of fusiform gyrus and precuneus, whereas an emotional face-matching task showed differential activation of the cuneus depending on *CYP2D6* genotype.[109] Furthermore, a 5% decreased glucose uptake in the insula has been found in CYP2D6 intermediate metabolizers (IMs, $n = 6$) compared with EMs ($n = 11$, $P = 0.03$).[110] Overall, studies on the relationship between behavior and *CYP2D6* genotype have encompassed relatively few subjects and originate from a limited number of research groups. Further studies are needed before we can conclude a role for CYP2D6 in behavior and brain function.

CYP2C9 and non-steroidal anti-inflammatory drugs (NSAIDs)

The effect of *CYP2C9* genotype on the risk of gastrointestinal bleedings during non-steroidal anti-inflammatory drug treatment is at present ambiguous. A smaller meta-analysis of three studies[111] indicated an increased OR of 1.8 (95% CI, 1.2–2.5) for variant *CYP2C9* alleles (mainly *CYP2C9*2* and **3*). However, a few additional studies have rather added to the confusion by suggesting that the link between *CYP2C9* genotype and bleeding risk is completely open.[112] The non-steroidal anti-inflammatory drugs flurbiprofen and celecoxib have, however, without firm reasons, received FDA drug label information regarding CYP2C9, stating that known or suspected CYP2C9 poor metabolizers should administer the drugs with caution and in poor metabolizers (that is *CYP2C9*3/*3*) half the lowest recommended dose of celecoxib should be considered as the starting treatment.

PHASE II ENZYMES

UGT1A1, irinotecan and endogenous functions

Irinotecan is a chemotherapeutic used in combination treatments of mainly colorectal cancer. Excessive levels of irinotecan's bioactive metabolite, SN-38, can lead to severe neutropenia and this effect has been shown more pronounced in patients with the *UGT1A1*28* allele, which carries an extended promoter repeat causing reduced UGT1A1 transcription and activity (see Sim and Ingelman-Sundberg[1]). The risk of neutropenia in *UGT1A1*28/*28* subjects compared with carriers of none or one *UGT1A1*28* allele was shown in a meta-analysis of a total of 1998 irinotecan-treated patients to be as significant in low dose (RR = 2.4, 95% CI, 1.3–4.4) as in medium-dose patients (RR = 2.0, 95% CI, 1.6–2.5), whereas the risk was significantly increased in high-dose patients (RR = 7.2, 95% CI, 3.1–16.8).[113] Owing to the increased risk of neutropenia in *UGT1A1*28* carriers, the FDA has since 2005 recommended genotyping for *UGT1A1*28* to select subjects benefiting from a lower initial irinotecan dose, although genetic testing is not required. Homozygosity for the *UGT1A1*28* allele (>20% of subjects in certain populations) causes benign hyperbilirubinemia (Gilbert's syndrome) due to a decreased rate of bilirubin conjugation by UGT1A1, and more detrimental *UGT1A1* alleles can cause the more severe symptoms observed in Crigler–Najjar Syndrome.[114] As expected, *UGT1A1* was identified as the main component to influence serum bilirubin levels in GWA studies[115–117] (Table 2). These findings have also been demonstrated in humanized mice carrying the *UGT1A1*28* allele, which resemble subjects with Gilberts syndrome in terms of mild jaundice caused by increased bilirubin levels.[118] Thus, the link between *UGT1A1* polymorphisms and bilirubin levels is firmly established.

Thiopurine methyltransferase (TPMT) and thiopurine drugs

TPMT methylates the thiopurine drug 6-mercaptopurine (6-MP) that is used directly or administered as a prodrug (azathioprine) for the treatment of, for example, leukemia and chronic inflammatory disease such as Crohn's disease. Excessive levels of 6-MP can cause myelosuppression and myelotoxicity and blood count is normally monitored during treatment. TPMT is highly involved in 6-MP metabolism and TMPT activity and *TPMT* genotype is known to affect the risk of toxicity. TPMT activity can be phenotyped or genotype-predicted, but the sensitivity for genotyping analyses in predicting reduced TPMT phenotypes has been ambiguous. Recently, heterozygosity or homozygosity for variant *TPMT* alleles were shown to yield odds ratios for leukopenia of 4.3 (95% CI, 2.7–6.9) and 20.8 (95% CI, 3.4–126. 9), based on 18 and 5 studies, respectively.[119] In fact, TPMT genotyping or phenotyping (TPMT activity in red blood cells) is recommended by the FDA.

CONCLUSIONS

The field of DME polymorphism continuously develops and recently more substantial evidence has been obtained for the clinically most significant polymorphisms (see summarizing Figure 1). Indeed the recent studies have emphasized the importance of *CYP2C19* polymorphism for the therapeutic effects of clopidogrel, and the role of *CYP2D6* polymorphism for tamoxifen treatment appears to be relevant. The *CYP2C9* polymorphism is relevant in particular, for predicting patients requiring low doses of warfarin, but is of lower importance than *VKORC1* and demographic factors. The analgesic and side effects of codeine are influenced by *CYP2D6* polymorphism, whereas the effect of *CYP2D6* genotype on antidepressant response is without any firm evidence. It is, however, important to clarify the relation between CYP2D6 UMs and suicide behavior, especially in the light of recent reports on effects of *CYP2D6* genotype on brain perfusion and brain glucose metabolism. Good evidence for the influence of *CYP3A5* polymorphism on dosing of the immunosuppressive agent tacrolimus are at hand, and regarding phase II enzymes, anticancer treatment with mercaptopurines and irinotecan is important in relation to the polymorphism of *TPMT* and *UGT1A1*, respectively. Furthermore, interesting links between *CYP1A2* variation and caffeine intake as well as blood pressure has been emphasized recently, as has also the previously debated association of *CYP2A6* genotype with cigarette consumption.

The need for clarification of the cost-benefit of all these associations in the clinical setting remains an issue. At present, it is difficult to conclude which tests should be required, but recent research in the field encompassing much larger studies, where also a whole genome perspective is addressed, is the accurate way in order to be able to make firm and cost-effective recommendations for the drug treatment in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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