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Pharmacogenetic biomarkers as tools for improved drug therapy; emphasis on the cytochrome P450 system

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ABSTRACT

Important interindividual differences in drug pharmacokinetics cause absence of drug response or adverse drug reactions in significant fractions of the populations. The identification of the major enzymes participating, and the elucidation of the genetic basis for this variation in particular among cytochromes P450, provide tools for a personalized medicine treatment, which can make drug therapy much more effective at a lower cost. Much of the pioneering work linking drug metabolizing phenotype to genetic polymorphism among the P450 enzymes has been carried out at Karolinska Institutet. In this review we give a background and description of this work as well as the important implications for future medicine.

1. Introduction

Drug treatment is often inefficient. Only 30–60% of patients respond properly to treatment with antidepressants, beta-blockers, statins and antipsychotics (cf. [1]). Furthermore, adverse drug reactions (ADRs) frequently occur and cause about 7% of all hospital admissions, a frequency that is increased to 30% in elderly subjects above 70 years of age [2]. The ADRs cause on average 2 days of prolonged hospital visit and has been estimated to account for 100,000 deaths annually in the US (cf. [1]). It appears that the frequency of serious ADRs reported to the Food and Drug Administration (FDA) has doubled during the time period 1998–2005 [3] whereas the prescription of drugs has only increased by about 20% during the same time period. The major factor known today for interindividual differences in drug response is variable pharmacokinetics, which is mainly due to differences in the activity of cytochrome P450 enzymes involved in the metabolism of clinically used drugs. This area has been in focus of research at Karolinska Institutet since the mid-1970s and in the current presentation we describe some major achievements in this area and their clinically important aspects.

2. Cytochromes P450

The cytochrome P450 enzymes are important for the metabolism of both endogenous and exogenous compounds. There are 57 active genes in the human genome and enzymes in families 1–3 are particularly active in the detoxification of exogenous chemicals, whereas P450s in families 4–51 are mainly active in the metabolism of endogenous compounds like sterols, steroids, bile acids and fatty acids. At Karolinska Institutet, research in the P450 area was conducted from the mid-1970s by the groups of Henry Danielsson, Ingemar Björkhem and Jan-Åke Gustafsson as well as by the senior author of this review (Magnus Ingelman-Sundberg). Henry Danielsson in collaboration with Kjell Wikwall focused on enzymes and pathways involved in bile acid formation from cholesterol, whereas Ingemar Björkhem expressed his main interest in the field of neurosterols and P450 hydroxylations [4]. Jan-Åke Gustafsson was mainly interested in the mechanisms behind the sex differences of steroid metabolism in rodents [5]. At the same time period Magnus Ingelman-Sundberg characterized the membrane integration of the P450 system into the microsomal membrane and its interaction with the redox partners, in addition to isolating and cloning the ethanol inducible P4502E1 and showing its importance for development of alcoholic liver disease (cf. [6]).

3. Cytochrome P450 and drug metabolism

Interindividual differences in response to a xenobiotic was perhaps first described by Pythagoras in 510 BC. He noted that some individuals developed haemolytic anaemia in response to fava bean ingestion. In 1902, Gorrod and Oxon [7] suggested genetic components being of importance in biochemical processes and they suggested that interindividual differences in ADRs were due to enzyme deficiencies, an idea further emphasized by Motulsky in 1957 [8], and in 1959 Vogel [9] coined the term pharmacogenetics. Today it is known that the difference in drug metabolism is the major factor causing interindividual differences to drug exposure.

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Table 1
Drug metabolizing P450 phenotypes and polymorphic cytochrome P450 alleles of importance for unfavourable drug response.

Phenotype	Genetic basis	Clinical consequences	Examples of alleles causing the phenotype	Examples of clinical consequences
Ultrarapid metaboliser (UM)	More than 2 active gene copies on the same allele, or increased expression of a single gene	Lack of response of the parent drug Increased ADRs due to increased metabolite or active drug production	*CYP2C19∗17*, *CYP2D6∗1/∗2 x N* (gene duplication/ multi-duplication)	CYP2C19: increased bleeding risk with clopidogrel CYP2D6: non-response of antiemetics, antidepressants and increased suicidal risk. ADRs after codeine and tramadol treatment
Extensive metaboliser (EM)	2 functional alleles	Ordinary response	*CYP2C9∗1*, *CYP2C19∗1*, *CYP2D6∗1*	Normal metabolism
Intermediate metaboliser (IM)	1 defective allele or 2 partially defective alleles	Increased concentration of parent drug Decreased metabolite formation	*CYP2C9∗2*, *CYP2D6∗10*, *CYP2D6∗41*	Reduced response to tamoxifen and to analgesic treatment
Poor metaboliser (PM)	2 defective alleles	Higher levels of the parent drug Increased risk for ADRs	*CYP2C9∗3*, *CYP2C19∗2*, *CYP2C19∗3*, *CYP2D6∗4*, *CYP2D6∗5*	Increased ADRs Reduced response to analgesics and tamoxifen

In respect to this, cytochrome P450s, in particular CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP2B6, have a central role and are responsible for about 75% of the phase I metabolism of clinically used drugs. In total this estimates to about 60% of all drug elimination excretion and metabolism [10]. About 40% of the drug metabolism is mainly carried out by the highly polymorphic enzymes CYP2C9, CYP2C19 and CYP2D6 (Table 1). The genetic bases for the polymorphism in these genes are single nucleotide polymorphisms (SNPs), insertions and deletions (in/dels), and copy number variations (CNVs). The resulting phenotypes are ultrarapid metabolisers (UMs), extensive metabolisers (EMs), intermediate metabolisers (IMs) and poor metabolisers (PMs) (see Table 1.) The clinically most important phenotype and globally most distributed [11,12] is the UM phenotype. It causes lack of response at ordinary dose regimens and can also cause the formation of toxic metabolites and excess levels of the active drug in the case of treatment with prodrugs. Subjects being PMs have increased risk of adverse drug reactions and have the risk of getting no effect using drugs requiring activation by the enzyme in question. The identification of the variant alleles causing these phenotypes is a major task and in total about 360 different functional P450 alleles have been identified. A crucial tool in this work is the CYP-allele web page (see Section 4).

4. The human CYP-allele nomenclature database

The CYP-allele web page (The Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee) is hosted by us at Karolinska Institutet (www.cypalleles.ki.se) and forms a database for the international nomenclature of P450 alleles. We continuously get new submissions to this page and the submissions are peer reviewed before publication on the web site which often precedes the publication in the scientific papers. The number of visits is relatively constant over time and amounts to about 36,000 per year. The web site currently encompasses variant alleles of 29 human cytochrome P450 genes and since 2008 also of NADPH cytochrome P450 reductase (POR), the electron donor for P450 enzymes. The decision to include POR together with the CYP-allele nomenclature was based on the proven effect of POR mutations on the enzyme activity of P450s with endogenous function in hormone biosynthesis, thus implying the high probability of POR mutations affecting P450 enzymes involved in drug metabolism as well, which is an evolving area of focus. The *CYP2B6*, *CYP2C9*, *CYP2C19* and *CYP2D6* genes are particularly polymorphic with 29, 34, 26 and 78 functionally different alleles, respectively. Besides literature references and links to the dbSNP database, links to papers with allele frequencies are also presented.

5. CYP2D6

The polymorphic metabolism of the CYP2D6 substrates like debrisoquine, nortriptyline and desimipramine was early recognized. In 1967, Folke Sjöqvist and collaborators from Karolinska Institutet reported a high interindividual variability to metabolise nortriptyline and desimipramine [13]. They observed tremendous interindividual differences in the plasma levels of the drugs, following administration of the same dosage. Subsequently, two poor metabolisers were identified. A basic point at that time was to examine to how much of this variation was of environmental or genetic origin. In this, Folke Sjöqvist and Balzar Alexandersson were innovative and carried out a twin study in 1969 that clearly showed a genetic cause for the poor metaboliser phenotype [14]. This contribution by Sjöqvist and colleagues was indeed very important and pioneering, although subsequent experiments carried out by Bob Smith and Michel Eichelbaum (cf. [15]) in 1975 has perhaps inappropriately received more emphasis in the literature. The explanation of the genetic basis for absence of debrisoquine metabolism evident in a fraction of the European population was elucidated by Urs Meyer and Frank Gonzalez who cloned the *CYP2D6* gene and in 1990 identified the major defect allele *CYP2D6∗4* that carries a mutation leading to defective splicing [16,17]. In Orientals, it was known that there were no subjects with absent metabolism, but that in general Asians metabolise CYP2D6 substrates at a slower rate. In collaboration with Leif Bertilsson and Folke Sjöqvist we were able to elucidate the genetic basis behind this slower metabolism by the identification of the *CYP2D6∗10* variant allele in 1994 [18] which have mutations in the PPGP region at the NH_2-terminal that is important for folding of the enzyme. Interestingly, this variant is the most common allele in Asians and causes pharmacological effects, e.g., decreased effect of tamoxifen in breast cancer patients [19].

At Karolinska Institutet it is evident that the collaboration between the clinical pharmacologists at Huddinge University Hospital and our group at the Solna Campus has been very successful during the years. The translational aspect of science has been well taken care of since the clinical observations can be analyzed at a molecular genetic level early on. One interesting discovery based on our collaboration was the identification of the ultrarapid metaboliser phenotype caused by *CYP2D6* gene duplications. The history behind this, given in detail in Ingelman-Sundberg [15] and Johansson and Ingelman-Sundberg [20], was that a French research group opposed our size identification of the Chinese XbaI haplotype carrying the *CYP2D6∗10* allele. To answer to this, a retrospective screening of the fragment sizes using a lower density of the agarose gel was carried out and revealed samples with much higher

molecular weight DNA. Subsequent EcoRI restriction revealed that there were multiple *CYP2D6* gene copies on the same allele, and this constituted the first example of stable gene duplication and amplification in the human genome [21]. Interestingly, already in 1985, Leif Bertilsson and collaborators at Huddinge University Hospital had described a case with surprisingly rapid metabolism of nortriptyline [22]. A retrospective screening for this *CYP2D6* gene duplication revealed that the subject carried three active CYP2D6 gene copies, thus explaining the lack of antidepressant response [23]. Further investigations in this line has shown that patients carrying *CYP2D6* gene duplications are highly overrepresented among subjects not being responsive to antidepressant therapy [24,25]. Interestingly, the impact of this genotype for successful antidepressant therapy has been highlighted recently in a study where Zachrisson et al. [26] evaluated the genotype in deaths caused by intoxications, suicides or natural reasons (Fig. 1). Here, *CYP2D6* gene duplications were found at a 9-fold higher frequency in suicide cases as compared to natural death cases, indicating that the UM subjects did not receive appropriate response to the antidepressant therapy. In general the *CYP2D6* genotype is of high importance and should be taken into account for to predict relevant dosing of both antidepressants and antipsychotics as reviewed by Kirchheiner et al. [27].

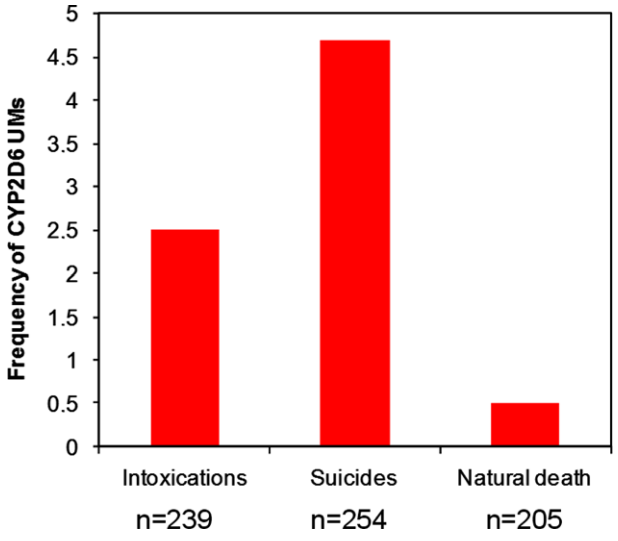

Fig. 1. Distribution of CYP2D6 ultrarapid metabolisers in forensic subjects where the death was caused by intoxications or suicides as compared to natural deaths. Data from Zachrisson et al. [26].

6. Karolinska Institutet in Addis Abeba

The senior author of this review was the chairman of the Karolinska Institutet Research and Training Committee in 1998–1994. One of the tasks was to build up an educational and research platform in Addis Abeba together with colleagues and with finances from Sarec/Sida. Among other initiatives a Masters programme in medicine was started and one student, Eleni Aklillu, was admitted to this programme. In her research work she brought many blood samples from Ethiopia to Karolinska Institutet for P450 allele analyses. Incidentally we found a very high frequency of *CYP2D6* duplications and multiduplications (29%) in this cohort [28], which stimulated us to investigate the frequency also in other countries. As a result also based on data from other laboratories, a high incidence was observed in Northern and Northeastern Africa, whereas the *CYP2D6* gene duplications in Asia turned out to be very rare. As a basis for the origin of this high frequency of duplications in Africa, we have suggested gene selection events caused by dietary pressure. Phenotyping of Ethiopians in Sweden and in Addis Abeba for debrisoquine metabolism revealed a lower rate of CYP2D6 metabolism in Ethiopians from Addis Abeba, as compared to those from Sweden despite the same genotype, indicating the inhibitory action of dietary components in Ethiopia [29]. This together with the fact that CYP2D6 has a high affinity for plant alkaloids, supports the proposed positive selection mechanism for the origin of the CYP2D6 duplications, whereby subjects carrying gene duplications were selected for survival during periods of starvation, since they had the ability to inactivate plant toxins to a larger extent and were thus able to tolerate a broader variety of plant species in their diet [30]. Because of migration from further South, the frequency of CYP2D6 duplications in Southern Europe is high (10–15%), whereas in Northern Europe the frequency of subjects with duplicated functional CYP2D6 genes is only 1–2% (cf. [12,30]).

7. CYP2C19

CYP2C19 metabolises drugs belonging to the antiulcer, antiepileptic and antidepressant classes. The molecular basis behind CYP2C19 poor metabolism has been known for more than 15 years and is mainly represented by the *CYP2C19*∗*2* allele in Europeans and in addition by *CYP2C19*∗*3* in Asians. It was however over 10 years later when the *CYP2C19*∗*17* allele, leading to an increased rate of transcription and increased metabolism, was discovered at the Karolinska Institutet [31]. The allele causes higher enzyme expression due to a polymorphic site creating a new binding site for transcription factors. The first identification of the variant allele

Table 2
Effect of the *CYP2C19*∗*17* allele on drug pharmacokinetics and clinical outcome.

Drug name	Drug type	Pharmacokinetics	Clinical effect	Reference
Chlorproguanil	Antimalaria (prodrug)	Incr. bioactivation (incr. chlorcycloguanil AUC and C_{max})	–	[39]
Clopidogrel	Antiplatelet (prodrug)	–	Decr. platelet aggregation *in vitro*, incr. risk of bleeding complications	[40] [34]
Escitalopram	Antidepressant	Decr. AUC, decr. serum concentration	–	[41] [42]
Imipramine	Antidepressant	Decr. plasma concentration	–	[43]
Mephenytoin	Probe drug (anticonvulsant)	Decr. MR	–	[31]
Omeprazole	Antiacid	Decr. MR, decr. AUC	–	[31] [41] [32]
Tamoxifen	Anticancer (prodrug)	–	Reduced risk of breast cancer relapse	[33]
Voriconazole	Antifungal	Decr. AUC	–	[44]

AUC, area under the plasma concentration time curve.
MR, metabolic ratio.

started as a project collaboration between us, the clinical pharmacologists at Huddinge University Hospital and Gemini Genomics. The company took on mini-sequencing to cover up to approximately 1.1 kb upstream of the translation start in DNA samples obtained from healthy volunteers phenotyped by omeprazole at Huddinge University Hospital in order to investigate SNPs in the 5′-upstream region. Four different haplotypes were identified of which one appeared to associate with higher CYP2C19 enzyme activity. This haplotype contained the −806C>T polymorphism that occurred at an allele frequency of 22% within the analyzed samples. The junior author (Sarah C. Sim) of the current review took on the work to characterize the mechanism behind this association as part of her doctoral work. She found −806C>T and −3402C>T in linkage equilibrium forming the *CYP2C19∗17* allele, and found some effects on CYP2C19 mRNA levels and enzyme metabolism *in vitro* using a human liver bank containing heterozygous, but no homozygous, samples. Electromobility shift assays revealed that the −806C>T but not the −3402C>T conversion recruited transcription factors that did not bind to the *CYP2C19∗1* equivalent. Reporter vectors containing the upstream sequence of the *CYP2C19∗1* or *CYP2C19∗17* allele were injected into the tail vein of mice together with a transfection reagent and we observed a 2-fold higher transcription in the *CYP2C19∗17* as compared to the *CYP2C19∗1* construct. We predicted a 35–40% lower omeprazole AUC in subjects homozygous for *CYP2C19∗17* as compared to *CYP2C19∗1* [31], an effect later shown to be 50% [32]. Subsequently, the *CYP2C19∗17* allele was found to be associated with increased metabolism of several common drugs, some of which are prodrugs like tamoxifen (breast cancer), chlorproguanil (malaria), and clopidogrel (thrombosis) (Table 2). Women on tamoxifen treatment for breast cancer being *CYP2C19∗17* carriers have a lower risk of relapse, an effect that is gene-dose dependent [33]. A similar gene-dose dependency has also been observed in patients on clopidogrel-treatment for prevention of stent thrombosis, whereby *CYP2C19∗17* carriers in comparison with *CYP2C19∗1/∗1* subjects are at successively increased risk of bleeding complications from 1 to 2 allele copies due to increased prodrug activation [34]. The *CYP2C19∗17* allele has also been shown to affect the blood concentration of antidepressants (escitalopram, imipramine) and the antifungal voriconazole (Table 2).

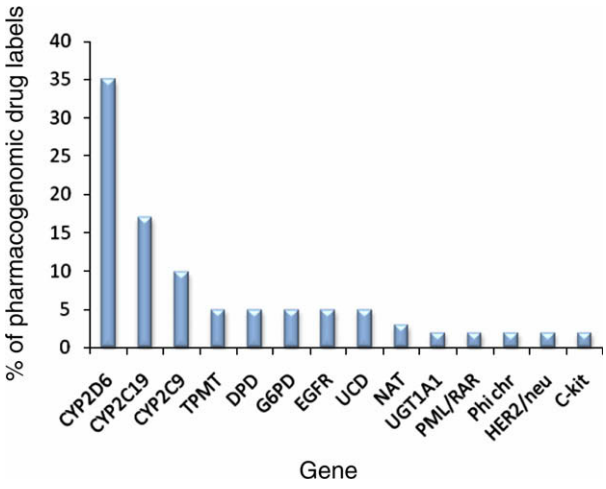

Fig. 2. Gene assignment of the current pharmacogenomic drug labels. Data from Frueh et al. [35].

8. Genetic biomarkers for a more efficient drug therapy

In general it is now emphasized that drug treatment should not be population-based but rather based on the individual patients' capability to respond to the drug treatment. Guidelines for pharmacogenomics in drug development have been published at FDA and are also to be released in 2010 by EMEA. The recommendations are to use pharmacogenomic biomarkers in different stages in (i) a mandatory manner, (ii) by recommendation, or (iii) for information purpose only. Of 1200 drug labels reviewed during the years 1945–2005, 121 contained pharmacogenomic information [35]. Of those, 69 drug labels referred to human genomic biomarkers where the polymorphic P450s CYP2C9, CYP2C19 and CYP2D6 accounted for in total 62% of the labels (Fig. 2). In recent years further genetic biomarkers have been identified that can predict the outcome of drug treatment. A summary has been given before [36] and an updated list is provided in Table 3. Among the examples where genetic P450 biomarkers play a role is tamoxifen treatment of breast cancer where defective *CYP2D6* alleles are associated with poorer treatment results due to the absence of formation of the active metabolite endoxifen [37], warfarin treatment where CYP2C9 has an important role for clearance of the drug, clopidogrel's bioactivation by CYP2C19 as mentioned above, and treatment of depression with tricyclic antidepressants in relation to CYP2D6 polymorphism. Among others it appears that specific HLA-alleles specifically predict the ADRs in response to, e.g., treatment with flucloxacillin [38], abacavir (cf. [36] and carbamazepine.

9. Conclusions

The knowledge about P450 enzyme polymorphism has turned out to be of great importance for drug development and for effective drug treatment (cf. Table 1). Interaction with the polymorphic P450 enzymes are screened for routinely early in drug development and yet more examples where novel drugs are influenced by P450 polymorphism in a clinically important way are detected.

Table 3
Some important pharmacogenomic biomarkers.

Drug	Treatment	Effect	Frequency	Genetic variation
Abacavir	HIV	Hypersensitivity	5%	*HLA-B∗5701*
Carbamazepine	Epilepsia	Hypersensitivity	10% (Asians)	*HLA-B∗1502*
Clopidogrel	Platelet aggregation	Bleedings	5–8%	*CYP2C19∗17*
Flucloxacillin	Infection	Liver injury	1–3%	*HLA-B∗5701*
Herceptin	Breast cancer	Response	20%	*Her2 (ERBB2)*
Iressa	Lung cancer	Response	10%	*EGFRTyrKinase*
Irinotecan	Colorectal cancer	Toxicity	5–10%	*UGT1A1*
6-Mercaptopurines	ALL; Morbus Crohn	Leukopenia	1%	*TPMT*
Simvastatin	High cholesterol	Myopathy	<1%	*OATP1B1*
Tamoxifen	Breast cancer	Response	7%	*CYP2D6 (CYP2C19∗17)*
Tricyclic antidepressants	Depression	Response	1–10%	*CYP2D6∗2xN*
Warfarin	Coagulation	Bleedings	25%	*CYP2C9/VKORC1*

ALL, acute lymphoblastic leukemia.

We believe that this information will be translated into the clinical routine situation in the years to come, the consequences of which will be of high benefit for millions of patients worldwide.

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