Pharmacogenomics in Relation to Tailor-made Drugs

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Abstract – The field of cytochrome P450 pharmacogenomics has progressed rapidly during the past 25 years. Recently, conjugating enzymes including sulfotransferase, acetyltransferase, glucuronosyltransferase and glutathione transferase have been also extensively studied. All the major human drug-metabolizing P450 enzymes and some conjugating enzymes have been identified and cloned, and the major gene variants that cause inter-individual variability in drug response and are related to adverse drug reactions have been identified. This information now provides the basis for the use of predictive pharmacogenomics to yield drug therapies that are more efficient and safer. Today, we understand which drugs warrant dosing based on pharmacogenomics to improve drug treatment. It is anticipated that genotyping could be used to personalize drug treatment for vast numbers of subjects, decreasing the cost of drug treatment and increasing the efficacy of drugs and health in general. It is assumed that such personalized P450 gene-based treatment which is so-called tailor(order)-made drug therapy would be relevant for 10-20% of all drug therapy in the future.

Keywords ☐ Pharmacogenomics, Tailor-made drug, Genetic polymorphism, Drug metabolizing enzymes, Idiosyncratic toxicity

INTRODUCTION

The Term "Pharmamcogenomics" is the study of genetically controlled variations in drug response. The key concepts and terms of genetic polymorphism include monogenic, polygenic and polymorphic. Monogenic variation is due to allelic variation at a single gene, and polygenic is due to variation at two or more genes.

Polymorphic variation is frequently occurring monogenic variation in more than 1%. Thus, characterization of the variants of the drug metabolizing enzymes will become increasingly useful in individualizing drug therapy, especially for drugs with a narrow therapeutic index (Fig. 1).

The polymorphic forms of P450s are responsible for the development of a significant number of adverse drug reactions (ADRs). According to Phillips *et al.* (2001), 56% of drugs that are cited in ADR studies are metabolized by polymorphic phase I enzymes, of which 86% are P450s. Only 20% of drugs that are substrates for non-polymorphic enzymes are in the

ADR reports. The costs of treating patients who possess polymorphic forms of P450s are much higher than those required to treat patients who possess non-polymorphic alleles. Furthermore, the number of non-responders to drug therapy is high and represents 30-60% of subjects treated with drugs (Spear *et al.*, 2001). Thus, knowledge about the P450 system is fundamental both for drug therapy and for drug development (Ingel-
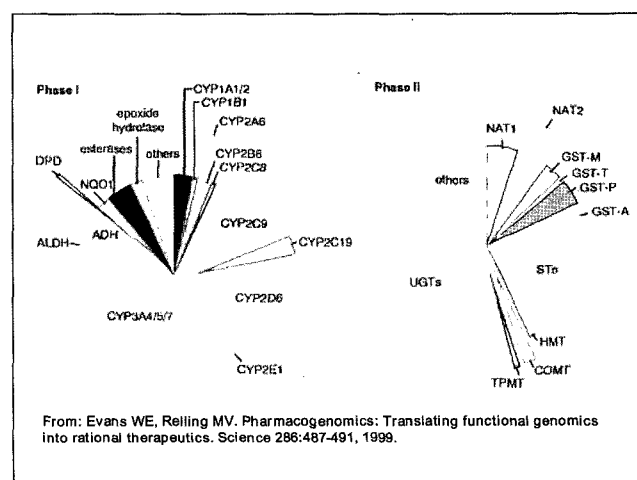

From: Evans WE, Relling MV. Pharmacogenomics: Translating functional genomics into rational therapeutics. Science 286:487-491, 1999.

Fig. 1. Genetic polymorphisms in drug metabolizing enzymes

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man-Sundberg, 2004; Weinshilboum, 2003) .

In this symposium, progress in the study of polymorphic P450s that are important for drug metabolism is presented with special emphasis on drug development and the clinical relevance of this research in terms of tailor (order)-made therapy .

GENETIC POLYMORPHISM OF P450

All genes encoding P450 enzymes in families 1-3 are polymorphic. The functional importance of the variant alleles, however, differs and the frequencies of their distribution in different ethnic groups also differ. Updated information can be found on the Human CYP allele Nomenclature Website (http://www. imm.ki.se/cypalleles).

Polymorphic enzymes such as CYP2C9, CYP2C19 and CYP2D6 mediate 40% of P450-mediated drug metabolism, which makes drug dosing problematic.

In general, four phenotypes can be identified: poor metabolizers (PMs), who lack the functional enzyme; intermediary metabolizers (IMs), who are heterozygous for one deficient allele or carry two alleles that cause reduced activity; extensive metabolizers (EMs), who have two normal alleles; and ultrarapid metabolizers (UMs), who have multiple gene copies, a trait that is dominantly inherited.

CYP2D6 dependent metabolism, indicating that the rate of metabolism for a certain drug can differ 1000-fold between phenotypes. Thus, the dosing required to achieve the same plasma levels of a drug metabolized mainly by CYP2D6, such as nortriptyline, differs 10-20-fold among individuals(Fig. 2). Despite this extensive variation in metabolic capacity among

individuals, dosing is, at present, principally population based. Namely, doses are based on the plasma levels of the drug obtained on average in the population at a certain dosage.

CYP3A4 is responsible for approximately 40-45% of all drug metabolism in phase I. This enzyme is highly conserved across different individuals and essentially no functionally variant forms have been observed in Caucasians or Orientals (Van Schaik et al., 2003; Fukushima-Uesaki et al., 2004). However, there is a relatively high inter-individual variability in CYP3A4 activity, which has been suggested to be of genetic origin (Ozdemir et al., 2000). Major causes that underlie inter-individual variability in drug metabolism of course also include poor compliance, unfavorable drug–drug interactions and pathophysiological conditions, factors that are always of great importance for the understanding of sub-optimal drug therapy.

INDIVIDUAL VARIATION OF P450 ENZYMES

The observation that individuals who are genetically deficient in a particular P450 enzyme are poor metabolizers of one or more drugs illustrates a variety important principle-namely that the rate of elimination of drugs can be largely determined by a single P450 enzyme. This observation seems to contradict the fact that P450 enzymes have broad and overlapping substrate specificities. The resolution to this apparent paradox lies in the fact that, although more than one human P450 enzyme can catalyze the biotransformation of a xenobiotic, they may do so with markedly different affinities. Consequently, xenobiotic biotransformation in vivo, where only low substrate concentrations are usually achieved, is often determined by the P450 enzyme with the highest affinity(lowest apparent Km) for the xenobiotic. For example, the N-demethylation of diazepam and the 5-hydroxylation of omeprazole are both catalyzed by two human P450 enzymes, namely CYP2C19 and CYP3A4. However, these reactions are catalyzed by CYP3A4 with such low affinity that the N-demethylation of diazepam and the 5-hydroxylation of omeprazole in vivo appear to be dominated by CYP2C19(Kato and Yamazoe, 1994). When several P450 enzymes catalyze the same reaction, their relative contribution to xenobiotic biotransformation is determined by the kinetic parameter, Vmax/Km, which is a measure of in vitro intrinsic clearance at low substrate concentrations(<10 percent of Km).
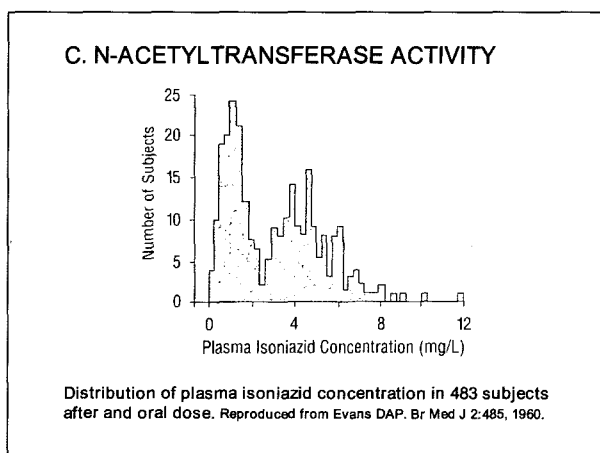

C. N-ACETYLTRANSFERASE ACTIVITY

Distribution of plasma isoniazid concentration in 483 subjects after and oral dose. Reproduced from Evans DAP. Br Med J 2:485, 1960.

Fig. 2. Dose requirement for nortriptyline in patients with different CYP2D6 phenotypes(From: Mayer U. Lancet 356:1667, 2000)

GENETIC POLYMORPHISM
OF CHOLINESTERASES

Pseudocholinesterase is a tetrameric glycoprotein(Mr 324kDa) containing four identical subunits, each having one catalytic site. The enzyme hydrolyzes succinylcholine, mivacurium, procaine, chlorpropaine, tetracaine, cocaine, heroin and other drugs. The duration of action of the muscle relaxant succinylcholine is determined by serum pseudocholinesterase. In some individuals (2 perent of Caucaciuans), succinylcholine causes prolonged muscular relaxation and apnea, which led to the discovery of an atypical form of pseudocholinesterase (Asp$_{70}$---Gly$_{70}$)(La Du, 1992; Lockridge, 1992).

Although this atypical enzyme has markedly diminished activity toward succinylcholine (which is the genetic basis for the exaggerated response to this muscle relaxant in affected individuals), it nevertheless has appreciable activity toward other substrates, such as acetylcholine and benzoylcholine. The normal and atypical pseudocholinesterases are equally sensitive to the inhibitory effect of certain organophosphates, but the atypical enzyme is relatively resistant to the inhibitory effect of dibucaine, a local anesthesic, which forms the basis of a diagnostic test for atypical psudocholinesterase (Fig. 3). The discovery of atypical psudocholinesterase is of historical interest because it ushered in a new field of pharmacogenetics. Since the initial discovery of atypical psudocholinsterase in late 1950s, several allelic variants of the enzyme have been identified.

GENETIC POLYMORPHISM OF CONJUGATING ENZYMES

The N-acetylation of xenobiotics is catalyzed by N-acetyltransferases and requires the cofactor acetyl-coenzyme A (acetyl-
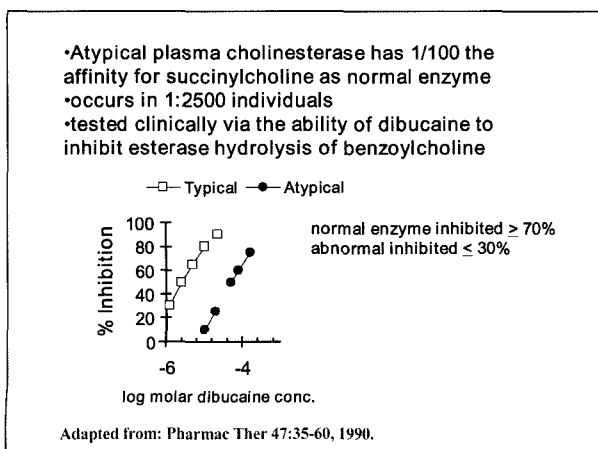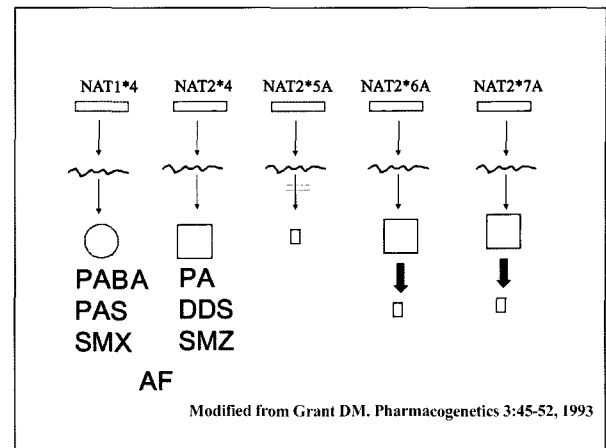
Fig. 4. Genetic isoforms of N-acetyltransferase

CoA). N-Acetyltransferases are cytosolic enzymes found in liver and many other tissues of most mammalian species, with the notable exception of the dog, which are unable to acetylate xenobiotics. In contrast to other xenobiotic-biotransforming enzymes, the number of N-acetyltransferases is limited (Vatsis et al., 2000). Humans, rabbits, and hamsters express only two N-acetyltransferases, known as NAT1 and NAT2, whereas mice express three distinct forms of the enzymes, namely NAT1, NAT2, and NAT3. NAT is the official gene symbol for arylamine N-acetyltransferase(EC 2.3.1.5)(Fig. 4).

A polymorphism of NAT2 (N-acetyltransferase 2) was one of the first to be found to have a genetic basis in a conjugating drug-metabolizing enzyme some 50 years ago. This isoform is involved in the metabolism of about 16 common drugs including isoniazid, procainamide, and caffeine. About 15 allelic variants have been identified, some of which are without functional effect, but others are associated with either reduced or absent catalytic activity. Considerable heterogeneity is present in the worldwide population frequency of these alleles, so that the slow-acetylator phenotype frequency is about 50% in American whites and blacks, 60% to 70% in North Europeans, but

•Atypical plasma cholinesterase has 1/100 the affinity for succinylcholine as normal enzyme
•occurs in 1:2500 individuals
•tested clinically via the ability of dibucaine to inhibit esterase hydrolysis of benzoylcholine

—□— Typical —●— Atypical

normal enzyme inhibited ≥ 70%
abnormal inhibited ≤ 30%

log molar dibucaine conc.

Adapted from: Pharmac Ther 47:35-60, 1990.

Fig. 3. Inhibitory effect of dibucaine on plasma cholinesterase

Table I. Ethnic differences in the distribution of acetylator phenotype

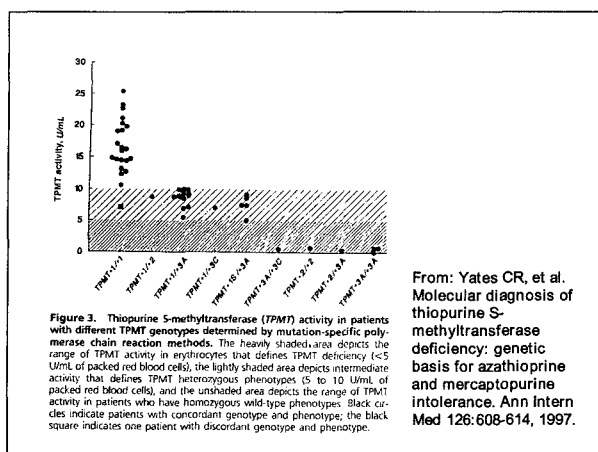| Population	% Slow	% Hetero Fast	% Homo Fast
South Indians	59	35.6	5.4
Caucasians	58.6	35.9	5.5
Blacks	54.6	38.6	6.8
Eskimos	10.5	43.8	45.7
Japanese	12	45.3	42.7
Chinese	22	49.8	28.2

From: Kalow. Clin Pharmacokinet 7: 373-4000, 1982.

Figure 3. Thiopurine S-methyltransferase (TPMT) activity in patients with different TPMT genotypes determined by mutation-specific polymerase chain reaction methods. The heavily shaded area depicts the range of TPMT activity in erythrocytes that defines TPMT deficiency (<5 U/mL of packed red blood cells); the lightly shaded area depicts intermediate activity that defines TPMT heterozygous phenotypes (5 to 10 U/mL of packed red blood cells), and the unshaded area depicts the range of TPMT activity in patients who have homozygous wild-type phenotypes. Black circles indicate patients with concordant genotype and phenotype; the black square indicates one patient with discordant genotype and phenotype.

From: Yates CR, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. Ann Intern Med 126:608-614, 1997.

Fig. 5. Thioprine 5-methyltransferase(TPMT) activity in patients with different TPMT genotypes determined by mutation-specific polymerase chain reaction method.

Table II. Debrisoquine phenotype in subjects with different CYP2D6 genotypes

Genotype	# of Subjects	Metabolic Ratio
CYP2D6wt/(CYP2D6L)$_2$	9	0.33
CYP2D6wt/CYP2D6wt	12	1.50
CYP2D6wt/CYP2D6(A or B)	9	2.14
CYP2D6B/CYP2D6B	6	48.84

(*CYP2D6L*)$_2$ - gene duplication; *CYP2D6A* - single base deletion CYP2D6B - multiple point mutations

Data from: Agundez JG et al. Clin Pharmacol Ther 57: 265, 1995

only 5% to 10% in Southeast Asians (Table I). It has been speculated that acetylator phenotype may be associated with environmental agent-induced disease such as bladder and colorectal cancer; however, definitive evidence is not yet available.

Similarly, genetic variability in the catalytic activity of glutathione S-transferases(GSTs) may be linked to individual susceptibility to the diseases. Thiopurine methyltransferase (TPMT) is clinically important in the metabolism of 6-mercaptopurine, the active metabolite of azathioprine (Fig. 5). As a results, homozygotes for alleles encoding inactive TPMT(0.3% to 1% of the population) predictably exhibit severe pancytopenia if given standard doses of azathioprine; such patients typically can be treated with 10% to 15% of the usual dose (Yates *et al.*, 1997).

PHARMACOLOGIC IMPLICATIONS OF GENETIC POLYMORPHISM

The Pharmacologic effects of certain drugs are exaggerated in a significant percentage of the population due to a heritable deficiency in a P450 enzyme(Tucker, 1994; Mayer, 1994; Smith *et al.*, 1998). The two major polymorphically expressed P450 enzymes are CYP2D6 and CYP2C19, although allelic variants have been described for nearly all the human P450 enzymes involved in xenobiotic biotransformation(Smith *et al.*, 1998).

Individuals lacking CYP2D6 and 2C19 were initially identified as poor metabolizers of debrisoquine and S-mephenytoin, respectively. However, because each P450 enzyme has a broad substrate specificity, each genetic defect affects the metabolism

of several drugs. The incidence of the poor-metabolizer phenotype varies among different ethnic groups. For example, 10 percent of Caucasians are poor metabolizers of debrisoquine(an antihypertentive drug metabolized by CYP2D6), whereas less than 1 percent of Japanese subjects are defective in CYP2D6 activity (Table II).

In contract, 20 percent of Japanese subjects are poor metabolizers of S-mephenytoin(an anticonvulsant metabolized by CYP2C19), whereas less than 5 percent of caucasianss are so affected. On some Pacific isolands, as many as 70 percent of the population are CYP2C19 poor metabolizers (Keneko *et al.*, 1999). Some individuals have been identified as poor metabolizers of tolbutamide and phenytoin, both of which are metabolized by CYP2C9., or as poor metabolizers of coumarin or phenacetin, which are metabolized by CYP2A6 and CYP1A2, respectively. However, the incidence of each of these phenotypes is apparently less than 1 percent of the populations examined to date.

TOXICOLOGIC IMPLICATIONS OF TROGLITAZONE

The idiosyncratic drug reaction due to the genetic polymorphism is one of the serious problem in pharmaceutical development. A class of thiazolidinediones (troglitazone, resiglitazone and pioglitazoneZ) has recently been introduced into the market as new drugs for the treatment of insulin-resistant diabetes mellitus. Troglitazone was withdrawn from the market in 2000, however, due to an incidence of rare but severe hepatotoxicity including death in some patients (Table III). The hepatotoxicity was later diagnosed as an idiosyncratic, hepatocellular injury. The idiosyncratic hepatotoxicity is not likely a class-effect since there has been no such cases reported for rosiglitazone and pioglitazone as of yet.

A tremendous amount of safety data collected from the

Table III. Chjaracteristics of triglitazone hepatotoxicity

1. No relation to the sex, age, dose level and concomitant drugs
2. Observed within 3~5 months
3. Increase in serum transaminases (GPT, GOT) precedes the increase in total bilirubin
4. Low or no increase in ALP, γ-GTP activities
5. Not reproducible in experimental animals
6. Diagnosed as an idiosyncratic, hepatocellular injury-type hepatotoxicity.

Table IV. Genotype of GSTT1 and GSTM1

GST gene		Control Patients		Patients with Hepatotoxicity	
GSTT1	GSTM1	n	(%)	n	(%)
wild	wild	25	(29)	3	(12)
wild	null	27	(32)	7	(28)
null	wild	20	(24)	5	(20)
null	null	13	(15)	10	(40)
Total		85	(100)	25	(100)

$p=0.043$

Data from: I. Watanabe and T. Koga *et al. Clin. Pharm.* Ther. 73, 435-455 (2003)

experimental animals before regulatory approval failed to predict the adverse reaction of this drug. Toyoda *et al.*(2001) reported that troglitazone causes apoptosis when added to cultured rat hepatocytes. Since this phenomenon was observed only at clinically irrelevant, high concentrations of troglitazone (>25 μM) in varoius cell types, including animal and human hepatocytes, apoptosis was not considered to the causal factor of the idiosyncratic toxicity.

Funk *et al.* (2001) reported that the sulfo-conjugate of troglitazone inhibits the canalicular. bile export pump(Bsep), possibly causing the accumulation of bile acids in the hepatocytes and cholestasis. This was also considered an unlikely mechanism since the hepatotoxic patients exhibited signs of hepatocellular injury but not particularly, those of cholestasis. Most hepatotoxins are regarded to produce chemically reactive metabolites, which covalently bind to physiologically important macromolecules unless inactivated by various scavenger enzymes.

Kassahun *et al.* (2001) demonstrated that CYP3A4 catalyzes the production of chemically reactive forms of troglitazone metabolites, i.e., the quinone methide, sulfenic acid- andÉø-ketoisocyanate-forms, which were all detected in vitro as glutathione conjugates. Yamamoto *et al.* (2002) reported the production of an epoxide-form metabolite of troglitazone using the CYP3A4 expression system. A long-term troglitazone-treatment was suggested to increase the likelihood for these reactions since troglitazone induces CYP3A4, which is the isoform most commonly present in the human liver.

Gene analysis showed that 40% of the case patients possessed the hull genotype of both GSTT1 and GSTM1 (Table IV). The results indicated that a patient-specific deficiency in the scavenger enzymes but not the amount of reactive metabolites produced could be the underlying cause of the hepatotoxicity (Watanabe *et al.*,2003). However, another mechanism is quite likely involved since 15% of the control patients also had the same genotype. It is known that most cases of the idiosyncratic hepatotoxicity are accompanied with some form oif immune reactions. Some kind of danger signal is thought to induce the immunoreactions, and this signal, in the case of troglitazone, may be the signal inducing apoptotic cytotoxicity. This signal may also induce the proliferation of cytotoxic T-lymphocytes, the cells that discriminate others from self, which then kill the drug-modified hepatocytes.

CONCLUSION AND FUTURE PERSPECTIVES

It is to be assumed that the major allelic variants of P450 genes of clinical importance have now been identified. However, further genetic reasons that underlie variable P450 expression might remain to be identified in other genes encoding, for example, proteins with regulatory functions such as transcription factors. Furthermore, RNA-regulating proteins might to be relevant and add to the complexity of the field. In addition, P450 expression polymorphism might not only exist at the genomic level because alternative

Splicing ((Bracco and Kearsey, 2003) has already been shown to generate variable P450s. With respect to depression and psychosis, Kirchheiner *et al.* (in press) have carried out an impressive investigation and concluded that receptor polymorphism is of no value for predicting drug therapy; instead, they suggest that dosing of 50-60% of the drugs used in such therapy is dependent, to a large extent, on the CYP2D6 and CYP2C19 genotype. At present, predictive genotyping for P450s in the clinic does not occur routinely for many reasons (Pirmohamed and Park, 2003).

P450 polymorphisms are emphasized in the Food and Drug Administration (FDA) draft guidelines (Lesko *et al.*, 2003) and clinical trials could be stratified according to P450 genotype with reduced costs as a consequence. All major drug companies take the pharmacogenomic aspect of P450s into account during drug development, and termination of the development of a candidate that has high affinity for a polymorphic P450

enzyme occurs if pharmacologically competitive candidates that are not substrates for the polymorphic enzymes are at hand. This might in the long term decrease the problem of P450 polymorphism in future drug therapy.

Our knowledge about the benefits of predictive genotyping for a more effective therapy is increasing. Therefore, I believe that predictive genotyping for P450s will be routine for several specific drugs in the future. Based on the role of polymorphic P450s in drug metabolism, as shown by Kirchheiner *et al.* (in press), such action will improve the clinical efficacy of 10-20% of all drug therapy and reduce the incidence of ADRs by 10-15 %. However, other aspects that underlie inter-individual variability in drug metabolism, such as poor compliance, unfavorable drug-drug interactions and pathophysiological conditions, remain important and are often primary factors of concern in drug treatment.

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