

MOVING TOWARD GENETIC PROFILING IN PATIENT CARE: THE SCOPE AND RATIONALE OF PHARMACOGENETIC/ECOGENETIC INVESTIGATION

G. ALVAN, L. BERTILSSON, M.-L. DAHL, M. INGELMAN-SUNDBERG, AND F. SJÖQVIST

Division of Clinical Pharmacology, Department of Medical Laboratory Science and Technology, Huddinge University Hospital, S-141 86 Huddinge, Sweden (G.A., L.B., M.-L.D., F.S.); and Division of Molecular Toxicology, Department of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (M.I.-S.)

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The topic of genetic profiling in patient care was recently reviewed in *Nature Biotechnology* under the title "Laying the foundations for personalised medicines" (Marshall, 1997). The prevailing principle of gathering statistical information about the general patient population and then applying the knowledge to treat the individuals is no longer sufficient. Providing "personalised medicines" should be based on a detailed knowledge at the genetic and molecular levels about disease traits and individual factors governing pharmacodynamic and pharmacokinetic variability. Only a few decades ago, pharmacotherapy was conceived as giving generally agreed doses of drugs of choice to the patients in a rather stereotypical manner. The need for individualization has since then been recognized, and much effort has been invested in a number of medical research fields to establish a scientific basis for individualization taking into account mechanisms of action, pharmacogenetics, drug metabolism, pharmacokinetic-pharmacodynamic relationships, therapeutic drug monitoring, treatment follow-up, and evaluation of adverse drug effects. The individual components of all these aspects on rational use of drugs are important and should be studied with the aim of improving drug therapy.

Genetic variability and selection directed toward the characters of the individuals are considered to be the fundament of the evolution and adaptation of living organisms to all environments where they are able to exist. The interplay between genetic constitution and other factors has consistently been emphasized. The true meaning of "heritage" is sometimes misunderstood. The fact that a character is inherited or has a genetic predisposition does not mean that it has to penetrate into the phenotype of the next generation or that parents necessarily need to share a quality that is obvious in their children.

Many characters may be conceived as continuous variables, and among these are diverse physical and intellectual capacities, talents for art, etc. However, they all go back to the genetic code and will only appear as continuous or even gaussian variables if a large enough number of factors is involved in their control and a large enough number of individuals is studied. When investigated in detail, however, most characters will show skewness or separation into different modes. This can be explained by the influence of particularly strong factors such as monogenic or oligogenic coding systems or the influence of singular environmental factors.

Many examples of characteristics such as eye color, blood groups, tissue antigens, etc. show discrete variation into separate groups. This is also true for certain drug-metabolizing enzymes. An early obser-

vation was that isoniazid might be slowly or rapidly acetylated (Evans et al., 1960). The acetylation polymorphism is important for a number of drugs, which include the sulfa compounds dapsone and sulfapyridine, the antihypertensive hydralazine, and the antiarrhythmic procainamide. It has been shown that dosage requirement, treatment efficacy, and the risk of adverse drug reactions are related to the genetic profile of being a slow or a rapid acetylator.

The most important drug-metabolizing enzyme family is the cytochrome P450 system. It comprises several enzymes that show distinct but partially overlapping substrate specificity (Ingelman-Sundberg et al., 1999). The individuality of the P450¹ enzymes, including their regulation, is the basis of enzyme-specific drug metabolism, interindividual variability in drug pharmacokinetics, and metabolic drug interactions.

Tricyclic antidepressants were early found to display vast interindividual variability in steady-state plasma concentrations. Figure 1 shows the plasma concentrations obtained in two extreme patients and in nine intermediates who participated in a small study of the pharmacokinetics of desmethylimipramine after multiple oral doses. Subject GD who had 36-fold higher plasma concentration of desmethylimipramine than the patient KD with the lowest concentration was phenotyped 18 years later and found to be a poor metabolizer of the pharmacogenetic probe drug debrisoquine (Sjöqvist and Bertilsson, 1984).

The Debrisoquine/Sparteine Hydroxylation Polymorphism (CYP2D6)

Debrisoquine was launched as an antihypertensive agent but is no longer on the market. It was found to induce orthostatic hypotension in a small percentage of healthy volunteers who took the drug for investigational purposes. The reason for the exaggerated effect in these subjects was found to be the lack of an enzyme almost exclusively responsible for the metabolic elimination of debrisoquine, and the affected subjects were classified as poor metabolizers of debrisoquine (Mahgoub et al., 1977). The enzyme was operationally named "debrisoquine hydroxylase" but is now known as CYP2D6. Independent studies showed that the oxidation of sparteine is catalyzed by the same enzyme (Eichelbaum et al., 1975, 1979). Very soon many drugs were shown to be metabolized by CYP2D6 (Table 1).

The character of being a poor (PM) or an extensive metabolizer (EM) of debrisoquine is controlled as an autosomal, recessive monogenic trait with the PM phenotype being the recessive alternative. The genetic heritability of the debrisoquine hydroxylation phenotype is very high (79%), while only 6% of all variability of the debrisoquine metabolic ratio could be ascribed to environmental or cultural factors (Steiner et al.,

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Send reprint requests to: Gunnar Alvan, M.D., Medical Products Agency, P.O. Box 26, 751 03 Uppsala, Sweden. E-mail: gunnar.alvan@mpa.se

¹ Abbreviations used are: P450, cytochrome P450; PM, poor metabolizer; EM, extensive metabolizer; D2, dopamine 2; 5HM, 5-hydroxymethyl tolterodine.

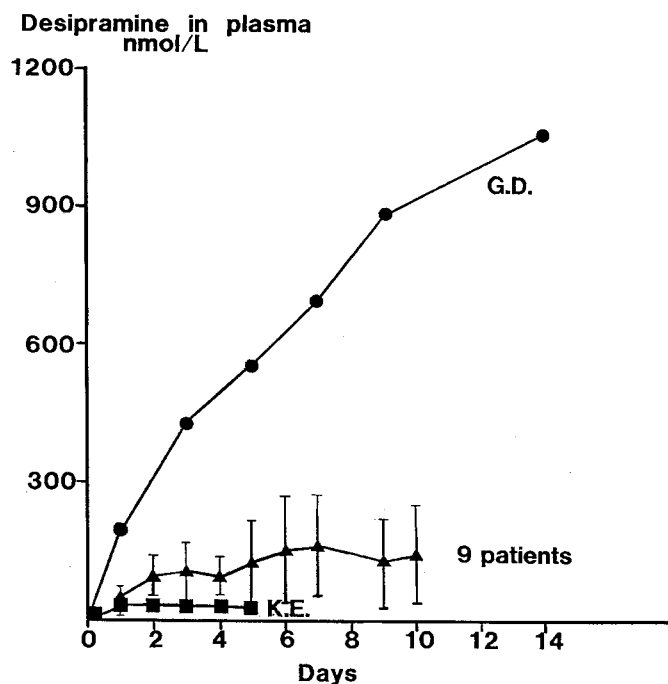


Fig. 1. Plasma concentrations of desmethylimipramine after dosing 25 mg t.i.d. to 11 patients (from Sjöqvist et al., 1967).

1985). The frequency of PMs of debrisoquine, based on a pooled European material of 8800 subjects, was 7.4% (Alvan et al., 1990).

There are now many examples of great influence of the CYP2D6 polymorphism on the disposition of drugs e.g., as illustrated by the antipsychotic haloperidol. This review is an account of our own experience. When a single oral dose of haloperidol was given to six EMs and six PMs of debrisoquine, a significantly slower elimination of the drug was found in PMs compared with EMs (Llerena et al., 1992) (Fig. 2).

Eight schizophrenic patients treated chronically with intramuscular injections of haloperidol decanoate every 4th week were studied (Nyberg et al., 1995). Plasma concentrations of haloperidol were much higher in one patient than in the other seven patients (Fig. 3A). This patient had the genotype CYP2D6*4/*4 and was thus a PM of debrisoquine, while the others were EMs. A positron emission tomography scan using the dopamine 2 receptor antagonist 11C-raclopride as a ligand was performed twice, 7 and 28 days after injection (Fig. 3B). The D2 receptor occupancy was very high, almost 80% in the PM patient at both 1 and 4 weeks. The EMs also had a high receptor occupancy 1 week after injection, but this decreased 4 weeks after injection. This study thus shows a relationship between the CYP2D6 genotype, the plasma concentration of haloperidol, and the effect on dopamine 2 receptors in the brain. In fact, the PM was the only patient to show extrapyramidal side effects of haloperidol.

It was early recognized that some rare subjects were outliers also to the left of the main distribution, i.e., displaying considerably more efficient metabolism of debrisoquine than the majority of EMs. The explanation for this finding was the existence of duplications and multiplications of the functional gene controlling the activity of CYP2D6 (Bertilsson et al., 1993; Johansson et al., 1993; Dahl et al., 1995). The distribution of CYP2D6 genotypes in relation to the debrisoquine metabolic ratio is shown in Fig. 4. The concept of the gene dose influencing the disposition of the parent drug and its hydroxylated was recently amply demonstrated for the tricyclic antidepressant nortriptyline (Dalen et al., 1998) (Fig. 5).

TABLE 1

Examples of drugs metabolized by CYP2D6

Tricyclic antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Nortriptyline
Other antidepressants
Fluoxetine
Fluvoxamine
Mianserin
Paroxetine
Venlafaxine
Neuroleptics
Haloperidol
Perphenazine
Zuclopenthixol
Thioridazine
Risperidone
Antiarrhythmics
Encainide
Flecainide
N-Propylajmaline
Propafenone
Sparteine
Betablockers
Alprenolol
Bufuralol
Metoprolol
Propranolol
Timolol
Others
Codeine
Debrisoquine
Dextromethorphan
Ethylmorphine
Nicotine
Perhexiline
Tolterodine
Tramadol

The first clinically useful method for analysis of the common CYP2D6 genotypes was developed by Heim and Meyer in 1990. The determination of the most abundant CYP2D6 mutations predicts the PMs' phenotype in European Caucasian volunteers with 92 to 99% accuracy (Broly et al., 1991; Dahl et al., 1992). The indications for genotyping methods as a complement to traditional therapeutic drug monitoring of antidepressants include identification of patients who are PMs to prevent supratherapeutic dosage regimen and concentration-dependent side effects, to differentiate between ultrarapid metabolism and poor compliance with the drug regimen, and to differentiate between pharmacogenetic and environmental determinants of drug metabolism by comparing genotype and phenotype (Dahl and Sjöqvist, 2000).

Genetic Profiling of a New Drug

The recently introduced antimuscarinic drug tolterodine, which is used to treat urinary bladder over activity, can serve as an instructive example of genetic profiling of a new drug. Tolterodine is a high-clearance drug with high first-pass metabolism. Its disposition was found (Brynne et al., 1998) to be highly dependent on the debrisoquine metabolic phenotype as shown in Fig. 6.

Interestingly, the metabolite 5-hydroxymethyl tolterodine (5HM) was detected in the EMs, but not in PMs. The strong association between tolterodine metabolism and CYP2D6 activity may appear as a great threat against a new drug candidate but fortunately in this case, the main metabolite is equipotent with the parent compound and considerably less protein bound. Consequently, there was no differ-

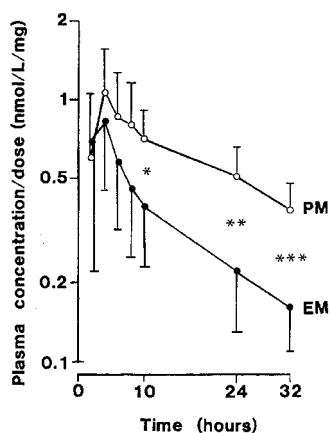
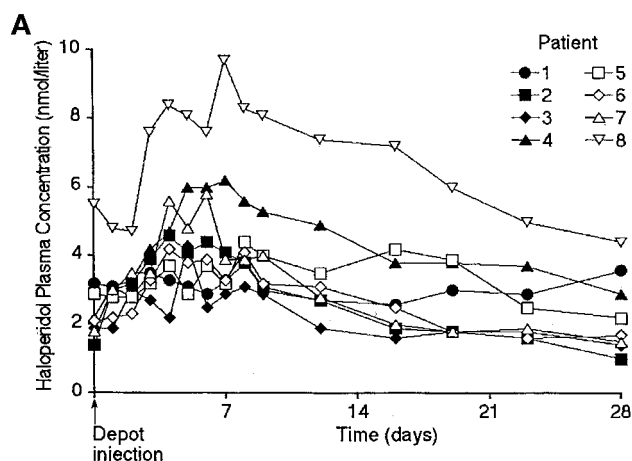


FIG. 2. Plasma concentrations per dose unit (mean, S.D.) versus time curves in six extensive metabolizers (filled circles) who received a single oral 4-mg dose of haloperidol and six poor metabolizers (open circles) who received 4- or 2-mg oral doses of haloperidol (from Llerena et al., 1992).



^aHaloperidol decanoate was administered on day 0.

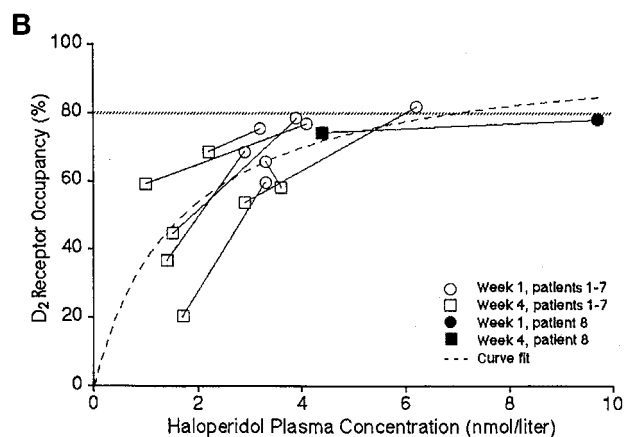


FIG. 3. Haloperidol plasma concentrations and receptor occupancy.

A, plasma concentrations of haloperidol in eight schizophrenic patients treated with haloperidol decanoate (from Nyberg et al., 1995). B, receptor occupancy plotted against plasma concentrations of haloperidol in schizophrenic patients 1 through 7 (extensive metabolizer genotype) and patient 8 (poor metabolizer genotype) 1 and 4 weeks after injection of haloperidol decanoate (from Nyberg et al., 1995).

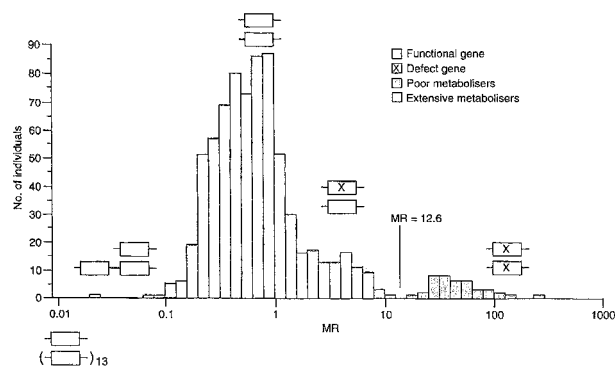


FIG. 4. Schematic presentation of the relationship between the debrisoquine metabolic ratio (MR) and the major cytochrome P450 (CYP) 2D6 genotypes causing altered CYP2D6 activity in healthy volunteers (from Bertilsson and Dahl, 1996).

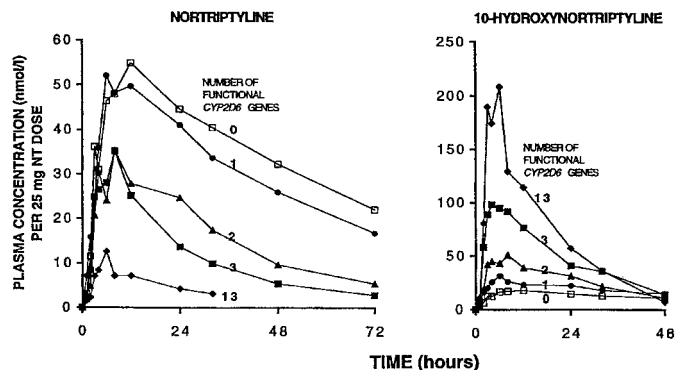


FIG. 5. Mean plasma concentrations of nortriptyline and 10-hydroxynortriptyline in different genotype groups after a single oral dose of nortriptyline.

The numerals close to the curves represent the numbers of functional CYP2D6 genes in each genotype group (from Dalén et al., 1998).

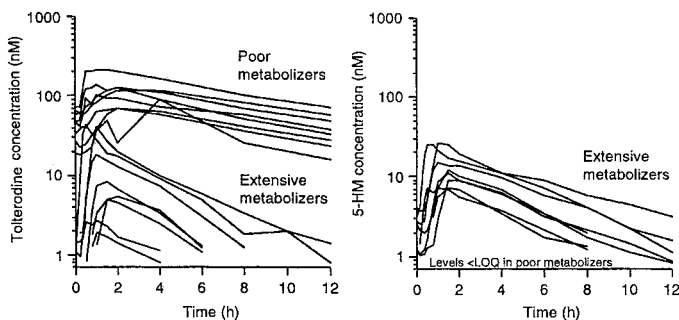


FIG. 6. Serum concentration-time profiles of tolterodine (left) and 5HM (right) during a dosage interval after 4 mg were given b.i.d. for 7 days in extensive ($n = 8$) and poor ($n = 8$) metabolizers of debrisoquine (from Brynne et al., 1998).

ence in the inhibition of salivation over 8 h between EMs and PMs (Fig. 7). Similar doses can thus be given to both phenotypes with seemingly equal clinical benefit.

S-Mephenytoin Hydroxylation Polymorphism (CYP2C19)

Another well investigated drug metabolic polymorphism, CYP2C19, may also serve as a good example of the potential of genetic profiling. This polymorphic enzyme is of great importance for the metabolism of the proton pump inhibitor omeprazole. Plasma concentrations after the first and the eighth daily doses of 20 mg to subjects with different genotypes are shown in Fig. 8.

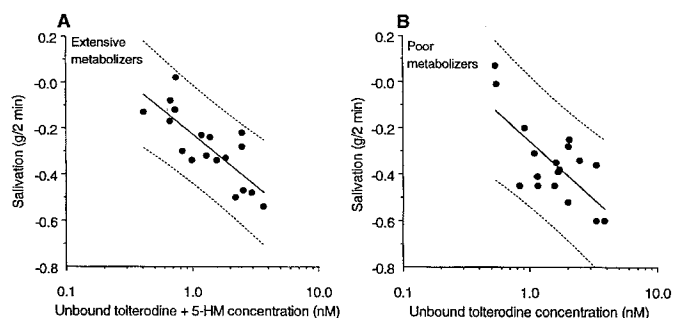


FIG. 7. Regression analysis and 95% confidence intervals of the median salivation effect (0–8 h) versus unbound serum tolterodine and 5HM combined (A) and tolterodine (B) concentration after oral doses, single, multiple, and during i.v. infusion of tolterodine L-tartrate in extensive and poor metabolizers of debrisoquine (from Brynne et al., 1998).

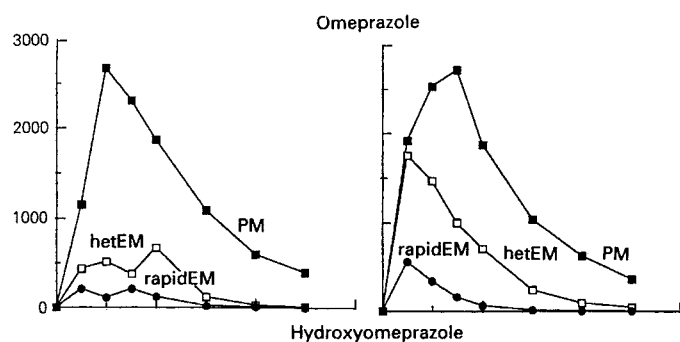


FIG. 8. Mean plasma concentrations of omeprazole in rapid extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers of *S*-mephenytoin after administration of the first (left) and the eighth (right) daily dose of 20 mg of omeprazole (from Chang et al., 1995).

The pharmacological response to omeprazole regarding gastrin secretion was evaluated in healthy subjects (Chang et al., 1995). There was no significant change in the gastrin secretion in any of the three different CYP2C19 genotype/phenotype groups after a single dose of omeprazole. The meal-stimulated gastrin plasma, however, were significantly increased in PMs of mephenytoin and in heterozygous EMs on the 8th day of omeprazole administration (Fig. 9). Similarly, in patients (Sagar, 1999) the intragastric pH did not differ between three genotypic groups (homozygous EMs, heterozygous EMs, and PMs) before treatment with omeprazole (day 0), while after 8 days of treatment with omeprazole the pH was significantly higher in heterozygous EMs and PMs compared with homozygous EM. Thus, the CYP2C19 genotype seems to influence the pharmacological effects of treatment for 8 days with omeprazole (Table 2).

Interethnic Variations

Realizing that the drug metabolic polymorphisms are part of and contribute to the interindividual variability seen in drug concentrations, one would like to assess any relevant differences between ethnic groups to consider adjustments of recommended standard doses (so called bridging studies). It is understood that differences within an ethnic group exceed those observed between ethnic groups. However, the mean population dose (starting dose) may differ between different ethnic groups. As an example, the activity of CYP2D6 as expressed by the debrisoquine metabolic ratio is higher in Swedish than in Chinese populations (Bertilsson et al., 1992) (Fig. 10). Differences between ethnic groups can also be seen in Table 3. Interestingly, the frequency of PMs (using the Caucasian antimode) is much lower among Chinese and other Oriental populations than among Swedes,

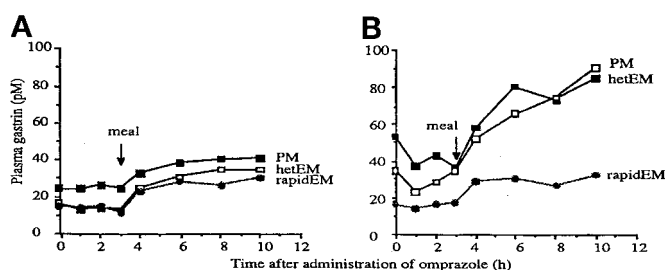


FIG. 9. Mean plasma gastrin levels in three phenotypic groups of CYP2C19 activity following a single 20-mg dose of omeprazole (A) and after the eighth daily dose of omeprazole (from Chang et al., 1995).

TABLE 2

Median intragastric pH (95% confidence interval) in the three CYP2C19 genotype groups before (day 0) and during (day 8) treatment with 20 mg of omeprazole daily

Data from Sagar (1999).

Genotype	n	Median Intra-gastric pH		
		Day 0	Day 8	P (Day 8 vs. Day 0)
wt/wt	11	1.1 (0.9–1.3)	3.1 (2.7–3.6)	0.003
wt/mut	12	1.4 (1.1–1.7)	5.5 (5.1–5.9)*	0.002
mut/mut ^a	2	1.3; 1.6	5.7; 6.6	
All	25	1.4 (1.2–1.5)	4.3 (3.6–5.2)	<0.0001

wt, wild type; mut, mutant.

* $p < 0.0001$ compared to wt/wt.

^a Individual values given.

while the overall capacity to metabolize debrisoquine and related compounds is lower among the Chinese. The reason for the low frequency of PM among Asians is the almost absence of the detrimental CYP2D6*4 allele, which is very frequent among Caucasians (Table 3). The reason for the generally lower capacity to metabolize debrisoquine is the high frequency of the CYP2D6*10 allele in the Chinese, 51% compared with only 1 to 2% in the European Caucasians (Table 3). This allele gives rise to an unstable enzyme and a much lower capacity to metabolize debrisoquine and other CYP2D6 substrates. This finding should in principle lead to a consideration to decrease the suitable starting or standard doses in Orientals, of all drugs that are to a large extent metabolized by CYP2D6.

A marked interethnic difference has also been noted between Caucasians and Orientals with regard to the distribution of the capacity to metabolize mephenytoin, the probe drug of CYP2C19, with an approximately 7-fold higher frequency of PMs in Orientals than in Caucasians (Bertilsson and Dahl, 1996). The conclusion is that Oriental patients obtain a functionally higher dose of omeprazole than do Caucasians if the same starting dose of 20 mg per day is applied. However, this does not seem to pose a problem as 20 mg daily is not therapeutically sufficient in many Caucasian patients, and the drug has a very wide safety margin, which allows a dose increase.

Genetic profiling has thus a great potential concerning the drug metabolic polymorphisms, as the PM may accumulate **higher than expected plasma concentrations** of parent compound and thus suffer **exaggerated effect/toxicity**. If the action of the drug is mediated by an active metabolite, there is a risk for therapeutic failure. The **extensive/ultrarapid metabolizer** may on the other hand get **insufficient drug concentrations** because a standard dose is too low compared with individual needs.

P450-Specific Drug Metabolic Interactions

As there is a rather strong specificity for different P450s among drugs viewed as chemical substrates, there is also an opportunity for

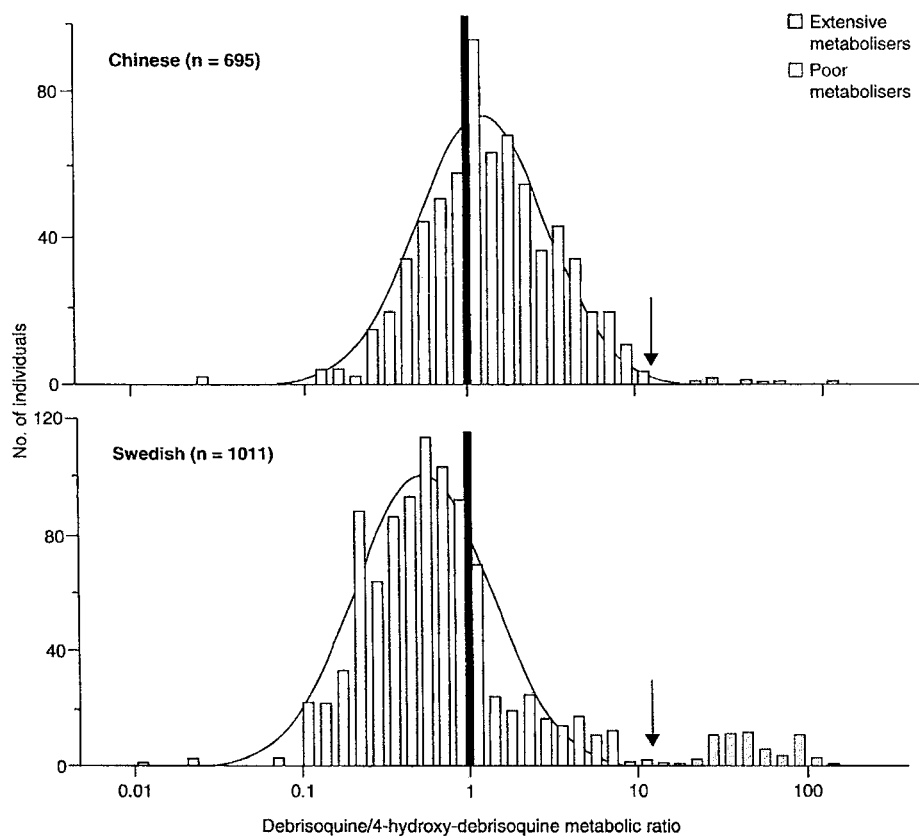


FIG. 10. Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio in Chinese and Swedish Caucasian healthy individuals.

The arrows indicate a metabolic ratio of 12.6, the antimode between extensive metabolizers and poor metabolizers as established in Caucasian populations. A thick line is drawn at a metabolic ratio of 1.0. Most Chinese extensive metabolizers have a ratio >1 , while most Swedish extensive metabolizers have a ratio <1 (from Bertilsson et al., 1992).

TABLE 3

Interethnic differences in the frequency of the major variant alleles of CYP2D6

Modified from Ingelman-Sundberg et al. (1999).

Allele	Mutation	Consequence	Allele Frequency			
			European Caucasian	Oriental	Black Africans	Ethiopians and Saudi Arabians
			%			
2D6*2xN	Gene duplication or multiduplication	Increased enzyme activity	1-5	0-2	2	10-16
2D6*4	Defective splicing	Inactive enzyme	12-21	1	2	1-4
2D6*5	Gene deletion	No enzyme	2-7	6	4	1-3
2D6*10	Pro34Ser, Ser486Thr	Unstable enzyme	1-2	51	6	3-9
2D6*17	Thr110Ile, Arg296Cys, Ser486Thr	Reduced affinity for substrates	0	N.D.	34	3-9

N.D., not determined.

competition for the active sites on the enzymes. Another aspect of genetic profiling is thus to predict and unravel this kind of interaction. Numerous such interactions have been described and listed in drug prescription reference sources. Figure 11 shows a systematic collection of investigated possible interactions of drugs with CYP2D6 (Brynne et al., 1999). With the exception of the β -blocker metoprolol and tolterodine, the other six drugs inhibited the metabolism of debrisoquine as indicated by an increased debrisoquine metabolic ratio. This approach can be used to systematically investigate the potential for clinically important enzyme-specific drug metabolic interactions.

Heterogeneity of Diseases

Genetic profiling offers a higher degree of understanding and resolution of many diseases that are traditionally regarded as diag-

nostic entities. However, conditions such as hypertension and affective and schizophrenic disorders are probably caused by numerous different genetic factors, and there is presently intense research trying to resolve the molecular background of these and other major diseases. An instructive example is the inherited lung and gastrointestinal disease cystic fibrosis, which was considered fairly homogeneous two decades ago. More than 900 mutations in a gene coding for the cystic fibrosis transmembrane regulator have now been described as the genetic cause of the disease. Cystic fibrosis transmembrane regulator is a chloride channel, and its impaired function is dependent on the individual mutations, which may call for individualized therapy. Functional polymorphisms have also been found for receptors that may be used as drug targets such as the dopamine D1-D5 receptors and six different serotonin receptors.

Work is done to improve the selection of antihypertensive therapy,

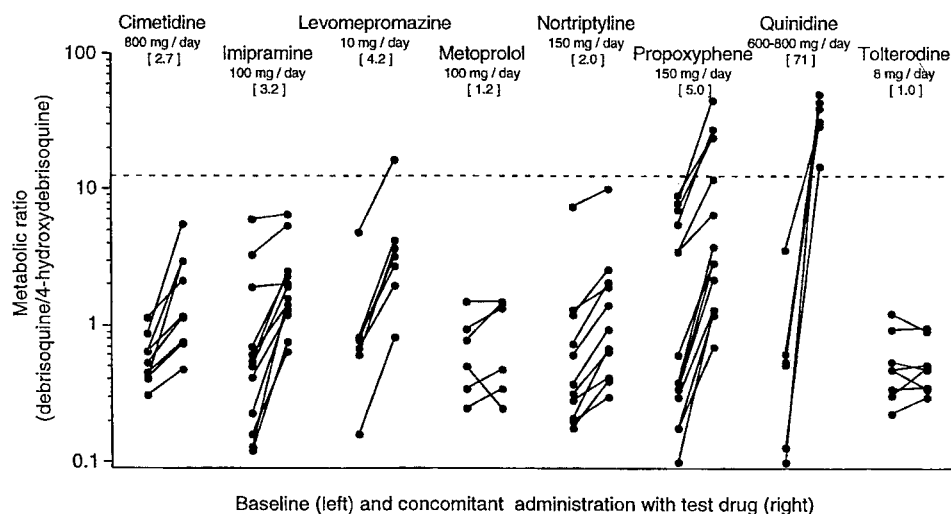


FIG. 11. Metabolic ratio of debrisoquine as a predictor of CYP2D6 interaction.

Each drug was given alone (left point in the pair) and together with debrisoquine (right point in the pair). The geometric mean values of concomitant administration (drug and debrisoquine) divided by the corresponding values in absence of drug is given within brackets under the daily dose of each drug (from Brynne et al., 1994).

and all the determinants of ischemic heart disease certainly offer new and more selective treatment options. Most hypertension is probably multifactorial, but in principal hypertension can also be caused by monogenic traits. Such hypertensive syndromes are Liddle's syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism. These hypertensive diseases have different genetic and molecular causes and should have different and specific treatment. Future research will likely discover more discrete and specifically treatable causes of hypertension and ischemic heart disease. The interplay between genes and environment certainly deserves attention since the superposition of environmental factors on genes that increase the risk of morbidity is often needed to precipitate overt disease.

Genetic profiling also offers a possibility for in depth analysis of some health hazards related to the use of drugs and other chemicals. For example, it has been suggested that patients who are deficient in CYP2C9, which is of main importance for the metabolic elimination of the anticoagulant warfarin, would be at an increased risk for warfarin-induced bleedings (Aithal et al., 1999). The authors wisely suggest genotyping in patients treated with warfarin to decrease the risk of this serious and sometimes fatal adverse drug effect. Awareness of such a specific risk factor would alert the drug prescriber to pay extra attention to the risk of warfarin overdosage.

In conclusion, genetic profiling increases the information about the individual patient. This information can be used to select proper treatment, to find a proper dose, and to explain and avoid drug interactions and adverse drug reactions.

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