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Genetic and environmental causes for interindividual variability in drug pharmacokinetics

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Abstract

The majority of phase I- and phase II-dependent drug metabolism is carried out by inducible and polymorphic enzymes, which can cause abolished, quantitatively or qualitatively altered or enhanced drug metabolism. Stable duplication, multiduplication or amplification of active genes, most likely in response to dietary components that have resulted in a selection of alleles with multiple genes, has been described for *CYP2D6*, *CYP2A6* and *GSTM1*. Several examples exist where subjects carrying certain alleles suffer from a lack of drug efficacy due to ultrarapid metabolism caused by multiple genes or by induction of gene expression, or alternatively, adverse effects from the drug treatment due to the presence of defective alleles. In addition, inhibition by other drugs and dietary components contribute to the important interindividual variability in drug metabolism and utilisation. Dosage requirements for several commonly used drugs that have a narrow therapeutic range can differ more than 20-fold dependent on the genotype or the enzyme expression status. The incidence of serious and fatal adverse drug reactions has been found to be very high among hospitalised patients. It is likely that predictive genotyping could avoid 10–20% of these deaths. Our knowledge in the field of pharmacogenetics has grown rapidly and can now be applied to both drug development and clinical practice. In the present contribution, an overview about our present knowledge on how the genetic constitution affects enzyme expression and drug efficacy is presented. Emphasis is given to different forms of cytochrome that are of importance for drug metabolism.

Keywords: Genetic polymorphism; Ultrarapid metabolism; Poor metabolisers; Drug metabolism; Genotyping; Pharmacogenetics

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1. Introduction

Interindividual variability in xenobiotic metabolism and drug response is extensive. The drug level in plasma can vary more than 1000-fold between two individuals having the same weight and with the same drug dosage. The causes for this variation are of genetic, physiological, pathophysiological and environmental origin. Genetic variability is known for drug absorption, drug metabolism and drug interactions with the receptors. This forms the basis for slow and rapid drug absorption, poor, efficient or ultrarapid drug metabolism and poor or efficient receptor interactions (see Fig. 1). Environmental influence includes induction and inhibition of drug transport and metabolism. Inhibition caused by, e.g., drug interactions, is an important factor for the outcome of the drug plasma levels reached. Ageing is known to result in less capacity for drug metabolism as well as less capacity to induce drug metabolising enzymes. In the past decade, genetic factors for this variability have received much emphasis. One could envision that the genetic factors would account for about 20–40% of the interindividual differences in drug metabolism and response, but for certain drugs or classes of drugs the genetic factors will be of utmost importance for the outcome of the drug therapy.

In the post-genomic area, a lot of useful information is available that provides the genetic basis for the discovery of new drug targets. The genetic information can also be used for better pharmacotherapy and involves the research fields of pharmacogenetics and pharmacogenomics. One might estimate that there are $\geq 50\,000$ different genes in the human genome. Earlier calculations of up to 140 000 genes were considered to be erroneous when the complete sequences of chromosomes 21 and 22 were ready, containing a surprisingly low number of genes. With a total of 3.12 billion nucleotides and the occurrence of Single Nucleotide Polymorphisms (SNPs) consisting of either base pair substitutions, nucleotide insertions or base deletions at a frequency of 1/1250 bp between two individuals, one can estimate the number of SNPs between two individuals to be about 2.5 million. Based on the genetic variability with respect to more rare SNPs,

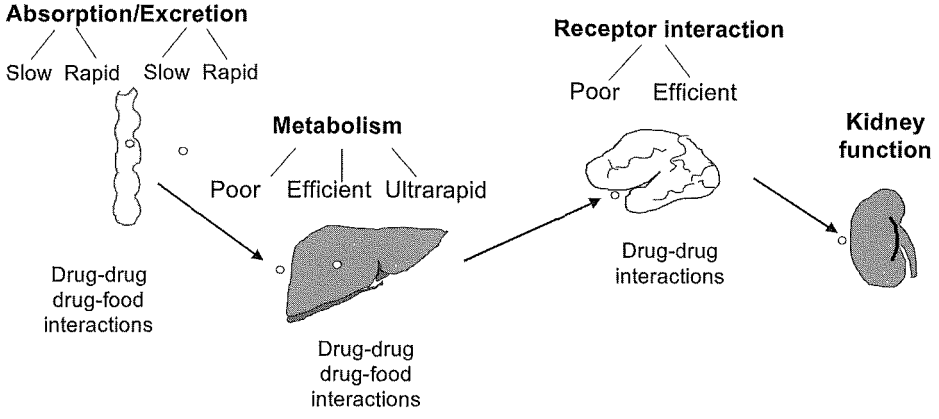

Fig. 1. Levels for interindividual variability in drug treatment.

taking hundreds of individuals into account, the actual number of SNPs might be between 5 and 15 million.

The number of reported SNPs rapidly increases. In March 2000, only about 100 000 SNPs were found in the databases but in November 15, 2000 as many as 1 593 067 human SNPs were present (http://www.ncbi.nlm.nih.gov/SNP/). Of those, it is clear that the majority do not have any function and are mainly located between the genes, intergenic SNPs (iSNPs). One could estimate the number of iSNPs to account to 5–15 million. Another class of SNPs is the perigenic SNPs (pSNPs) located in noncoding gene regions like the upstream regulatory regions in introns as well as consisting of silent mutations, and between 200 000 and 500 000 pSNPs might be present in the genome. In the coding regions, the cSNPs cause alteration in amino acids and an estimated number of those is between 50 000 and 100 000. Thus, the entire phenotype would be dependent on the individual composition of those giving theoretically a possibility for, with the assumption of two base variations on each SNP, $2^{100\,000}$, which is equal to more than $10^{30\,000}$ number of different individuals. It is clear that knowledge of all these cSNPs would be of utmost importance for the understanding of the genetic basis for disease as well as for differential response to drug treatment.

In case of applications in pharmacogenetics, it is clear that the information we have today is substantial and allows providing the patients with information that could facilitate an individualised therapy not only with respect to the choice of the drug but also with respect to the dose of specific drugs. In my opinion, pharmacogenomics is still in the very beginning; knowledge about genetic variation at the levels of drug targets and disease pathways is scarce and relatively few results have been provided. In addition, these data are sometimes incomplete, difficult to interpret or occasionally conflicting, but the field is still very promising and in the current review, I consider some important achievements in the field with emphasis on phase I enzymes. Some recent reviews include those of Ingelman-Sundberg et al. [1], Meyer [2] and Evans and Relling [3].

2. Adverse drug reactions (ADRs)

ADRs are more of a problem in drug treatment and drug development than previously thought. A meta-analysis revealed that serious adverse drug reactions occur among 6.7% of all hospitalised patients and that 0.32% of all hospitalised patients develop fatal adverse reactions, causing more than 100 000 deaths annually in the US [4]. Even though this study was criticised for having many old studies among those causing the majority of deaths, subsequent follow-up by the same authors, including studies in non-US countries, revealed a similar figure [5]. ADRs cause up to 5.5% of all hospital admissions [6], a figure recently verified in a UK study where 7.5% of all admissions were due to ADRs [7]. In Sweden it is evident that adverse drug reactions cause up to 13% of all admissions to internal medicine clinics [8]. The costs for ADR, including an average of 2 days of prolonged hospitalisation and reduced productivity, has been estimated to US$100 billion annually in the US [9].

In view of the relatively low frequency of responders of treatment with common drugs like β-blockers, SSRIs, tricyclic antidepressants and ACE-inhibitors of 10–50% and of the

high cost and serious consequences of ADRs, the idea of personalised drug therapy is attractive. Identification of the true responders in each case would not only avoid treatment of the nonresponders resulting to less cost for the drug treatment per se, but also reduce risk for ADRs with subsequent reduced costs for the society. As mentioned, the pharmacogenetics has been fairly well developed in the field of drug metabolising enzymes, but much less is known about functional genetic polymorphism of drug transporters and drug receptors.

3. Cytochrome *P*450

Sequencing of the human genome revealed 58 different human cytochrome *P*450 (*CYP*) genes according to David R. Nelsons' estimation (http://drnelson.utmem.edu/CytochromeP450.html). The majority of genes among the xenobiotic metabolising *P*450s in gene families 1–3 are polymorphic and, in addition, a large number of pseudogenes are present. In fact, it appears that only *CYP1A1* and *CYP2E1* among the xenobiotic metabolising *P*450s are relatively well-preserved and in essence, no functionally important mutations are present in these genes. The reason for this conservation might

Table 1
Major human polymorphic cytochrome *P*450 enzymes[a]

Enzyme	Major variant alleles	Mutation	Consequence	Allele frequency (%)	
				Caucassians	Orientals
CYP2A6	*CYP2A6*2*	L160H	inactive enzyme	1–3	0
	*CYP2A6*3*	2A6/2A7	not known	0	0
	*CYP2A6*4*	gene deletion	no enzyme	1	15
	*CYP2A6*5*	G479L	defect enzyme	0	1
CYP2C9	*CYP2C9*2*	R144C	reduced affinity for P450 reductase	8–13	0
	*CYP2C9*3*	I359L	altered substr spec	7–9	2–3
CYP2C19	*CYP2C19*2*	aber splice site	inactive enzyme	13	23–32
	*CYP2C19*3*	stop codon	inactive enzyme	0	6–10
CYP2D6	*CYP2D6*2xn*	gene dupl	increased activity	1–5	0–2
	*CYP2D6*4*	defective splic	inactive enzyme	12–21	1
	*CYP2D6*5*	gene deletion	no enzyme	4–6	6
	*CYP2D6*10*	P34S, S486T	unstable enzyme	1–2	50
	*CYP2D6*17*	T107I, R296C, S486T	reduced affinity for substrates	0	(in Blacks 34 %)
CYP2E1	*CYP2E1*2*	R76H	less enzyme expressed	0	1
	*CYP2E1*3*	V389I	no effects	<1	0
	*CYP2E1*4*	V179I	no effects	<1	nd
CYP3A4	*CYP3A4*2*	S222P	higher Km for subst	3	0
	*CYP3A4*3*	M445T	unknown	0	<1
	*CYP3A4*4*	I118V	decreased	0	<1
	*CYP3A4*5*	P218R	decreased	0	<1
	*CYP3A4*6*	831 insA	decreased	0	<1

[a] See http://imm.ki.se/CYPalleles for details and literature references. Allele frequencies are from Ingelman-Sundberg et al. [1] and Oscarson [26] and references therein.

be the endogenous importance of the corresponding enzymes. Concerning *CYP2J2*, *CYP2R1*, *CYP2S1*, *CYP2U1* and *CYP2W1*, no polymorphism has yet been described but is likely to appear in the literature in the near future. Thus, the interindividual distribution of these *P*450 forms is strikingly different and the extensive polymorphism, most likely to some extent, would not only result to dietary adaptation of different populations in the world but also to a genetic drift. No important endogenous substrates have been described for any of these polymorphic *P*450s and their primary function is most likely metabolism of dietary components. To facilitate for scientists in the field, a web page that contains continuously updated information regarding the polymorphic forms of *CYP*s has been created (www.imm.ki.se/CYP-alleles). A list of the most relevant variant forms of the *CYP*s of highest importance for the metabolism of drugs and other xenobiotics as well as their allele frequencies in Caucasians and Oriental populations is given in Table 1. As can be noted, most allelic forms are distributed with pronounced interethnic differences.

4. Consequences of mutations in the *CYP*-genes

The mutations in the *CYP* genes can cause enzyme products with abolished, reduced, altered or increased enzyme activity. Abolished enzyme activity is common where the whole gene has been deleted but is also seen as a consequence of mutations causing altered splicing, stop codons, abolished transcriptional start sites and deleterious amino acid changes. Mutations in substrate recognition sites (SRS) can cause the synthesis of enzymes with an altered substrate specificity as exemplified with *CYP2D6*17*, found entirely in black African populations, and with *CYP2C9*3*. Furthermore, mutations in the folding region can cause an altered protein folding and different substrate specificity as seen with *CYP2D6*10* [10].

The effect of the mutations on the substrate specificity studies are here much dependent on the expression system used for the enzyme variant. In our experience, the specific folding of enzyme variants is different in bacteria, yeast and mammalian cells, giving variable and often erroneous results. When studying the effect of the mutations on *CYP* function, one must bear in mind that folding of the enzymes can be different for two very similar polymorphic variants and that the mutations might influence each other in this respect. Thus, when studying the function of the *CYP2D6*17* allele, it was evident that the carriers of this variant had reduced capacity for metabolism of *CYP2D6* substrates [11], but introducing the unique mutation T107I had no effect on the properties of the enzyme [12]. It was found that only when R296C mutation was introduced together with T107I mutation that the enzyme exhibited altered properties for the drug substrates and a fivefold higher K_m was apparent.

Another very important aspect when studying polymorphic *CYP*s is the fact that the genotyping technique used for determination of the mutations on the genomic level is appropriate and correct. *CYP2A6* is the major nicotine oxidase and responsible for clearance of nicotine in vivo. In case of the *CYP2A6* gene, some studies have been published which have considered a relationship between the frequency of defect variants of the *CYP2A6* gene and smoking behaviour [13,14]. However, a very high frequency of

the *CYP2A6*2* and *CYP2A6*3* alleles were found in these studies. Re-examination of the genotype technique used by these authors revealed that the PCR-based genotyping did not specifically amplify the *CYP2A6* gene in the first step as originally thought due to a *CYP2A7* gene conversion event just 3′ of exon 9, where the reverse primer for the *CYP2A6* gene was supposed to bind [15]. Therefore, in the second mutation-specific PCR reactions, the pseudogene *CYP2A7* was amplified instead of giving erroneously high frequency of the *CYP2A6*2* and *CYP2A6*3* alleles. In fact, the *CYP2A6*3* allele has hitherto not been found in any subject investigated. Overall, the variant *CYP2A6* alleles are quite rare among Caucasians whereas *CYP2A6*4*, being a null allele, is quite common among Orientals (Table 2). In our laboratory today, five new different allelic forms of *CYP2A6* have been characterized mainly by the effort of Dr. Mikael Oscarson.

As mentioned, dose requirements differ in many cases tremendously between subjects carrying active forms of genes encoding drug metabolising enzymes as opposed to those lacking the appropriate enzyme. This is in particular important for, e.g., treatment with warfarin, a *CYP2C9* substrate and with tricyclic antidepressants, *CYP2D6* substrates. Daly et al. [16] reported on the increased bleedings among subjects carrying variant *CYP2C9* alleles. Dose requirements here were 0.5 mg/day among subjects with defective *CYP2C9* alleles as compared to 5–8 mg among subjects with the wt alleles. A dose dependency on the *CYP2C9* genotype but no increased frequency of bleedings among subjects with mutated *CYP2C9* alleles were found by Taube et al. [17].

Table 2
Examples of important pharmacogenetic influence of drug treatment

Drug transporters	
MDR-1	Functional polymorphism of relevance for the distribution of several drugs, further studies are needed.
Phase I enzymes	
CYP2A6	Nicotine clearance, smoking behaviour?
CYP2C9	Treatment with warfarin, losartan
CYP2C19	Long-term treatment with some gastric pump inhibitors and treatment with proguanil
CYP2D6	Treatment with dextromethorphan, nortryptilin, propafenone, desipramine, dexfenfluramine, haloperidol, perphenazine, perhexiline, codeine
DPD	Treatment with 5-fluorouracil
Phase II enzymes	
NAT-2	Treatment with isoniazide and hydralazine
TPMT	Treatment with 6-mercaptopurines
Drug receptors	
β_2-adrenergic receptor	Treatment with β_2-receptor agonists
ACE	Treatment with ACE inhibitors
Markers	
APOE4	Tacrine treatment in Alzheimers
CEPT	Treatment with pravastatin

5. Ultrarapid metabolizers

In contrast to poor metabolisers or efficient metabolisers, ultrarapid metabolisers (UMs) carry two or more active genes on the same allele [18]. The gene effect is striking and clearance of nortrityline or debrisoquine is proportional to the number of *CYP2D6* gene copies [19, 20]. Alleles with stably duplicated genes have now also been found for glutathione transferase M1 (*GSTM1*) and *CYP2A6*. Stable gene duplication, thus, seems to be a general phenomenon among the genes encoding drug metabolising enzymes.

Gene duplication do not occur unless it is beneficial for the organism. This raises the question about the origin of *CYP2D6* duplication, multiduplication and gene amplification, yielding alleles with 2, 3, 4, 5 or 13 gene copies (see Ref. [1]). A summary of the interethnic differences reveals that a focus of *CYP2D6* gene duplications has been in Ethiopia and Saudi Arabia with 20–30% of the population of this genotype. In contrast, very few subjects with gene duplications are seen in Asia and Northern Europe. In the Mediterranean area, about 10% of the population carry *CYP2D6* gene duplications, most likely as result of a Muslim migration to Gibraltar in about 700 AD. The distribution of the duplicated *CYP2D6* genes worldwide indicates that the gene duplication event has occurred rather recently, about 2000–5000 years ago. The *CYP2D6* gene is noninducible and it can be hypothesized that the duplication/amplification event has occurred as a result of dietary stress, as a manner for enzyme induction in response to environmental toxicant, mainly alkaloids which have a high affinity to *CYP2D6*.

6. Other phase I enzymes

Besides the *P*450 genes, other phase I enzymes are also polymorphic. Functional significance has been unravelled for alcohol dehydrogenases, acetaldehyde dehydrogenases as well as for dihydropyrimidine dehydrogenase (DPD). A polymorphism relevant to treatment with anticancer drugs is present in DPD. 5-Fluorouracil is metabolised by this enzyme and subjects with impaired enzyme activity due to inactivating gene mutations suffer from severely increased risk for adverse drug reactions.

7. Drug transport

With respect to polymorphism of drug transporters and the clinical outcome on drug treatment, much less is known. In total, about 15 allelic variants of the *MDR1* (P–gp) gene have been detected [21,22]. Recently, a silent mutation in *MDR1* (P–gp) has been associated to the rate of drug transport in the intestine [22], but the functional basis for this association was obscure since no functional mutation in the *MDR1* gene was described. However, recently, Kim et al. [21] found that a functional mutation Ala893Ser was often associated to the silent *C3435T* mutation (*MDR* * *2*) detected by Hoffmeyer et al. [22].This might provide a functional explanation for the polymorphism seen. Recently, several genes encoding drug transporters have been found in the MRP locus but the genetic polymorphism of this locus has to be worked out.

8. Polymorphic pharmacodynamics

As mentioned, an increased knowledge is now provided regarding the functional consequences of different receptor subtypes, although this area is by far not yet in a stage where clear-cut recommendations for choices of drugs and drug dosages can generally be made based on the receptor variant.

Among the most potentially interesting targets in development for genotype-based pharmacotherapy is the β_2-adrenergic receptor. Functional mutations affecting the stability of the receptor have been found at Arg16, affecting the stability of the receptor. The Gly16 variant is down-regulated to a great extent in response to ligand when expressed in recombinant cells. This has received support from in vivo studies where asthmatic children receiving albuterol had an increased broncodilatation if they were of a Arg16 genotype, consistent with the fact that this variant is less down-regulated than the Gly16 variant. Other studies of different designs have, however, failed to obtain such a relation. Thr164, where the mutant Ile164 forms, has a decreased affinity for many, but not all β-adrenergic receptor agonists. A similar polymorphism is seen at Arg389 on the β_1-adrenergic receptor where the mutant form (Gly389) has lower coupling efficiency with isoproterenol [23].

Studies of the β_2-adrenergic receptor is complicated by the fact that many upstream and coding region mutations occur at 13 different SNPs which are present, yielding a possibility of $2^{13}=8192$ different haplotypes. However, in a study of 54 controls from three different ethnic groups and 121 Caucasian asthmatics, only 12 different haplotypes were shown to occur [24]. Some of the SNPs, in particular in the upstream region, were in close linkage, whereas those in the open reading frame were not. Examination of the haplotype in relationship to the effect of a β_2-agonist on the forced expiratory volume (FEV) revealed that subjects with some haplotypes in combination responded to a higher extent. In addition, there was a difference in expression of the receptor haplotypes in *HEK293* cells both at the protein and mRNA level [24]. These results raises the possibility to use SNP haplotyping for predicting drug response as hypothesised by Roses [25], although the results with the β2 receptor has to be reproduced by other investigators and more examples are needed to exemplify this principle before it is possible to consider this as a feasible manner for genotype-based drug prescription.

9. Conclusions

Pharmacogenetics is only in the very beginning with respect to its use in clinical practice. Based on the very rapid development of the number of functionally important SNPs, it is conceivable that we, in the near future, will have information that allows individualised drug therapy based on the genetic constitution at a much higher resolution, which can be effectively used for a safer and more efficient pharmacotherapy. In Table 2, some important examples are given where we can apply pharmacogenetics already today. With respect to drug transport, the functional polymorphism of the P–gp (*MDR1*) gene provides an important topic for further studies when we now have the point for the functional polymorphism identified. In particular, it is relevant to study the effect on drug distribution in the brain. Concerning phase I metabolism, genotyping provides an

important tool for more efficient drug therapy using a limited number of specific drugs. These include warfarin (*CYP2C9*), tricyclic antidepressants (*CYP2D6*), codeine (*CYP2D6*), perphenazine (*CYP2D6*) for treatment of schizophrenia, and long-term treatment with omeprazole (*CYP2C19*) and related pump inhibitors. In addition, 5-fluorouracil treatment in relation to the polymorphism of dihydropyrimidine dehydrogenase is highly relevant for genotyping. Among the phase II enzymes, it is evident that predictive genotyping for deficiencies in the thiopyrinemethyltransferase gene is highly relevant for correct dosing of 6-mercaptopurines during treatment of leukemia and that NAT-2 genotyping is beneficial for prediction of side effects caused by isoniazide and hydralyzine. In other cases with respect to drug metabolising enzymes, more studies are needed before the impact of genotyping for the efficiency of drug therapy can be validated. On the receptor level, the most promising relationships has perhaps been found for treatment with β_2-adrenergic agonists and tacrine.

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Appendix A. Discussion 15

M. Pirmohamed: The first question is that we've known about the *CYP2D6* polymorphism for well over a decade. Why is it that you don't think that people are being genotyped or phenotyped before they go on 20% of drugs that are metabolised by *CYP2D6*? The second question is about the variability in induction. If you give the same dose of an inducer such as carbamazepine, you find that there is a great deal of variability in induction. Do you think that's all environmental, or is there a genetic component to that as well?

M. Ingelman-Sundberg: There is a lack of the methods and information out in the clinics, and there is a lack of validation of what the genetic polymorphism *CYP2D6* has caused. If the GP interacts with the patient, the patient should state that he or she gets better effects, or is more happy with a genotype-based treatment. Alternatively, the GP has to follow regulations which forces him to take genotyping into consideration. Neither of these points is valid for the drug prescription by the GP at present because there are no regulations and there are no clear cases spread in the general society where much benefit have been described as a consequence of genotype-based treatment. But in the future, when we can pinpoint the associations and be more focussed and do better validation studies, it will be more applied, and we also have cheaper genotyping tests. Regarding induction polymorphism, we haven't seen much of it yet because we have not yet examined the polymorphism of the relevant receptors and transcriptional factors. Some genetic evidence for induction polymorphism of *CYP1A2* has been described. However, e.g., PXR was just cloned a couple of years ago, and no one has described polymorphism

in this gene. Thus, I think there are a lot of genetic components for induction polymorphism that we haven't seen and identified yet.

P. Morgan: You make a good point that drug companies will now try and screen out *CYP2D6* substrate because of the the variability that there would be. But as you showed, a lot of the other *P*450s are showing polymorphism as well. Drugs have to be metabolised by something, and *CYP*s are going to metabolise a lot of drugs. Can you comment on the type of variability in oral clearance of those observed with some of the other *CYP*s, is it as large as with *CYP2D6*?

M. Ingelman-Sundberg: If you look at the polymorphism of three to four other *CYP*s, it's as large but of less clinical significance. Environmental factors drug–drug interactions can be of at least equal importance for the variation in clearance. If you consider two possible out-layers, the first, a rifampicin-treated patients who take, for example, midazolam, and as a second example, a ketoconazole-treated patient who takes the same drug, the level of difference you see in midazolam plasma concentrations is at least a hundred-fold. In my opinion, drug–drug interactions can be as important or more important than the genetic factors.

N. Holford: I'd like to come back to the issue of the *CYP2D6* duplication or multiplication. In your hypothesis, this is realted somehow to environmental stress. Just looking at the parts of the world that appear to be very nonstressed, it appears that Australia and New Zealand have no stress at all, in fact, nobody knows whether they are duplicated or not. Why do you think that Asia's a nonstress from the alkaloid point of view but Central Africa is?

M. Ingelman-Sundberg: The Asian population emerged from the African about 60 000 years ago and then moved away. In Ethiopia, you can count that this stress-causing gene duplications has been quite recent, about 5000 years ago. Something must have happened very recently in Ethiopia and accordingly this stress has not occurred in Asia where the *CYP* genotypes observed and most likely the result of a genetic drift. My current belief is that some specific alkaloids present in Ethiopian plants, which have a nanomolar affinity for *CYP2D6*, has caused a dietary-based gene stress and population selection in Ethiopia.

D. Mould: When you're doing drug development, it's very common for the oriental community, Japan in particular, to do a number of studies to see that the doses being administered are appropriate for Orientals. However, it seems to be uncommon to see a different dose regimen in the oriental community or in other countries. You gave a number of examples where the metabolism patterns would be expected to be grossly different in different racial populations, for instance in one case I would have expected to see differences in the African population. Yet again, the dose field seems to be unaffected even though the metabolism is quite different. I was just wondering if you could comment on this situation in terms of drug development strategies.

M. Ingelman-Sundberg: If you look at haloperidol, in the Asian population you have a specific *CYP2D6* variant, the **10*. It has a pro34ser mutation which causes an enzyme that is not properly folded. This means that in Orientals, they do have about 1/3–1/5 of the rate of *CYP2D6* metabolism as compared to Caucasians. Haloperidol is prescribed in Asia, just long before we identified this polymorphism, at 1/3 of the dose as we do in Caucasians. The Orientals adapted to the right dose drug therapy before we understood the genetics behind it. There are other important cases where you do would have an ethnic-specific

dose regimen. If you look at *CYP2C19*, where 25% of the Oriental population lack the enzyme, this polymorphism has a drastic effect on, e.g., omeprazole pharmacokinetics. At standard doses, you get about three- to four-fold higher plasma concentration in this population, a dose effect which no one takes into account. I think there are reasons to claim that clinical trials during development of some drugs, which are substrates for these polymorphic enzymes, should indeed be carried out in different ethnic populations.

K. Park: The question I'd like to raise is that warfarin's mixture of isomers, each of which are metabolised by a different *P*450 enzyme. If this was a new drug today, would you develop it as a single enantiomer, and if so which one would you choose?

M. Ingelman-Sundberg: If you asked me, I wouldn't develop it at all. There are other ways of developing drugs for the same purpose with better pharmacokinetics, and better targets today.

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