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Pharmacogenetics and Metabolism: Past, Present and Future

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1. Introduction

Throughout history, humanity has referred to toxic reactions in response to food, plants, and more recently, medications or drugs. **Pythagoras** is thought to be one of the first to observe that some individuals, but not all, would get sick after eating fava beans. Introduction of the complex term *pharmakon* (a word used to designate substances that may produce beneficial or harmful effects to human health) by Hippocratic physicians brought with it a paradox: a compound may be served both as a drug and a poison at the same time. As it is currently known, administration of a substance may offer higher risk of toxic effects than when administered at a lower dose. But then, what about a drug dosage that induces toxicity in a patient, treats another well and had no effects on the other? This and other important observations such as the understanding of metabolic variability have started to unravel the mysteries behind these phenomena. For example, the ancient observation why different outcomes were regularly observed after Greek soldiers ate fresh fava beans (Nebert 1999).

The concept of **'variability in metabolism'** claims that biochemical processes within the organism are responsible for transformation of compounds from food or medicines, and that this process could be different among subjects leading to a range of organic responses. Alexander Ure (1841) seems to have been the first to report organism's ability to convert an exogenously administered compound into one or more different metabolites. In the study entitled '*On Gouty Concretions with a New Method of Treatment*', Ure reported that benzoic acid was converted to hippuric acid by humans (Ure 1841). Then, it gradually began to be accepted that living systems have a "physiological chemistry" responsible for the modification of substances, and from the second part of 19th century, a significant number of metabolic pathways have been discovered.

At that time, however, the key answer to why there is individual variability in metabolism had not yet been answered, which only came to light after the rediscovery of Mendel´s study about hereditary around the turn of the 20th century. A well-known example to illustrate this was the influence of the genetic findings of William Bateson on studies of Sir Archibald Garrod about alkaptonuria and phenylketonuria presented in the book entitled "*Inborn Errors of Metabolism*" (Garrod 1909). In fact, the results founded by Garrod were a milestone to explanation of metabolic variability from a genetic perspective. Thereafter, some forerunners separately described series of observations that preceded the conceptualization of the Pharmacogenetics (PGx). In 1932, Arthur Fox found a remarkable variation in the ability of some individuals to

taste a foreign chemical phenylthiocarbamide (PTC) (the 'taste blindness') (Fox 1932). Interestingly, this finding was unexpectedly discovered when some of the PTC molecules escaped in to the air and Fox's co-worker C.R. Noller noticed a bitter taste, while Fox could not taste it. Intrigued by Fox's findings about bitter taste, L.H. Snyder published an important study (especially for the relevant quantity of participants) confirming the Fox's observation that some people perceive the bitter taste of PTC, while others do not. In addition, Snyder found that such non-tasting is a recessive genetic trait, and today it is one of the best-known Mendelian traits in human populations (Snyder 1932).

In a similar fashion, animal studies at that time also supported the genetic contribution in drug metabolism variability. Sawin and Glick (1943) in the study entitled "*Atropinesterase, a Genetically Determined Enzyme in the Rabbit*" demonstrated a genetically determined outcome in rabbits after ingestion of the belladonna leaves (Sawin & Glick 1943).

In the middle of 20th century, evidences necessary to support the transformation of the scattered "pharmacological heritability" in a new science finally appeared. First, Hettie Hughes described a relation between the level of isoniazid (an anti-tuberculosis drug) acetylation and occurrence of peripheral neuritis (Hughes et al. 1954), which absolutely was a landmark step for future demystification of the "one size fits all" system of drug prescribing. Another milestone in PGx was an independent investigation about death of patients caused by a generally safe, local anesthetic drug procaine (Kalow 1962). Further experiments enabled the authors to suggest that a genetically determined alteration in the enzyme structure may cause an abnormal and lethal low cholinesterase activity. The atypical enzyme does not hydrolyze the anesthetic with efficacy, resulting in a prolonged period of high levels of the drug in the blood and increased toxicity (Kalow 2005). Simultaneously, Alf Alving and co-workers observed that African-American soldiers presented an increased risk to develop acute haemolytic crises after primaquine (an antimalarial drug) administration, when compared with Caucasian ones (Clayman et al. 1952). As shown later, this sensitivity is caused by a genetically determined deficiency of glucose 6-phosphate dehydrogenase (G6PD), which alters erythrocyte metabolism (Alving et al. 1956). Thus, it took approximately 2,400 years to explain the Pythagoras observation about favism from a molecular perspective. It is now believed that defect in the *G6PD* gene is related with fava-induced hemolytic anemia in some individuals of Mediterranean descent.

Finally, opening a new era of pharmacological investigation, Arno Motulsky in 1957 published a masterpiece paper entitled "*Drug reactions, enzymes and biochemical genetics*", highlighting the genetic basis of "how hereditary gene-controlled enzymatic factors determine why, with identical exposure, certain individuals become 'sick', whereas others are not affected" (Motulsky 1957). The works of Kalow and Motulsky were (and still are) an unequivocal scientific catalyzer for understanding of the genetic influence in drug metabolism. Friedrich Vogel, a German Pharmacologist in 1959 was the first to coin the term 'Pharmacogenetics' (PGx) for the emergent new area of scientific discoveries, that unifies different conceptions on pharmacotherapy and xenobiotic-induced disease risk (Vogel 1959).

Despite the terms *Pharmacogenetics* and *Pharmacogenomics* are used interchangeably, most authors prefer to use PGx when inherited differences in drug response are being evaluated. On the other hand, Pharmacogenomics is usually used to study general aspects of drug response involving genomic technologies to determine a drug profile or even a new drug. Although is common association between PGx and drug metabolism variation, many others

inherited differences in drug response are investigated by PGx, such as polymorphisms in genes that encode molecules transporters (Vaalburg et al. 2005) and drug targets (Johnson & Liggett 2011; Maggo et al. 2011). For practical purposes, preference will be given to the use of the term Pharmacogenetics throughout this chapter.

2. Metabolizers subpopulations, a brief review

Since physiological responses associated with a particular drug have been linked to biochemical attributes in the body of the recipient, several studies have attempted to elucidate which factors modify the clinical response to a greater or lesser extent. There is now a general understanding that variability in the function of **drug-metabolizing enzymes (DME)** is responsible for many differences in the disposition and clinical consequences of drugs. Although it is a central issue to PGx, in clinical practice most decisions about a medicine prescription are mainly based on the classic factors responsible for drug variability, including co-existing disease (especially those that affect drug distribution, absorption or elimination), body mass, diet, alcohol intake, interaction with others drugs and mechanisms to improve patient compliance. In fact, all of these have been demonstrated to directly affect the indicated dose of the drug. However, they only partly explain why most major drugs are effective in only 25 to 60 percent of patients. Furthermore, taking into account patients with same physical and demographic characteristics, why does a standard dose is toxic to some patient but not to others? Why not all patients demonstrate the expected efficacy in drug treatment trials? Undoubtedly, these and many others questions opened the door for a new era of the personalized medicine and treatment perspectives (Nair 2010).

It is well-know that drug levels can be raised by increasing the dose or by more frequent administration in a non-responder patient. Conversely, if a higher plasmatic drug level with a standard dose administration is expected (in a patient with cirrhosis or malnutrition, for example), increasing the time of administration or suspending the dose may be a reasonable attitude. Although advances in medical technology and potential predictive models have improved the choice of dose, they are not yet sufficient to prevent high level of morbidity and mortality caused by **adverse drug reactions (ADR)**, as shown in the clinical practice (Wu et al. 2010). Thus, it is believed that the study of how genetic variation interface with drug metabolism, especially in genes codifying DMEs, may also lead to improve drug safety.

A variety of factors affecting the expression and activity of DMEs are classified into three major groups: **genetic factors**, **non-genetic host factors** (such as diseases, age, stress, obesity, physical exercise, etc.) and **environmental factors** (environmental pollutants, occupational chemicals, drugs, etc.). Recent studies clearly indicate that interindividual variation in drug metabolism is one of the most important causes of drug response differences. In general, common pharmacokinetic profile is a lighthouse for most prescribers in clinical practice. Figure 1A exemplify a simplified model of a drug biotransformation route. Most pharmaceuticals compounds or molecules (M1 in figure 1) when administrated orally are lipid-soluble enough to be reabsorbed (in the kidneys) and eliminated slowly in small amounts in an unchanged form in urine. Therefore, drug biotransformation by enzymes (represented by E1) has a key role in the control of plasmatic drug concentration. It should be remembered that the metabolites (M2) might also exert pharmacological effect (which will be discussed later). In addition, low activity of the

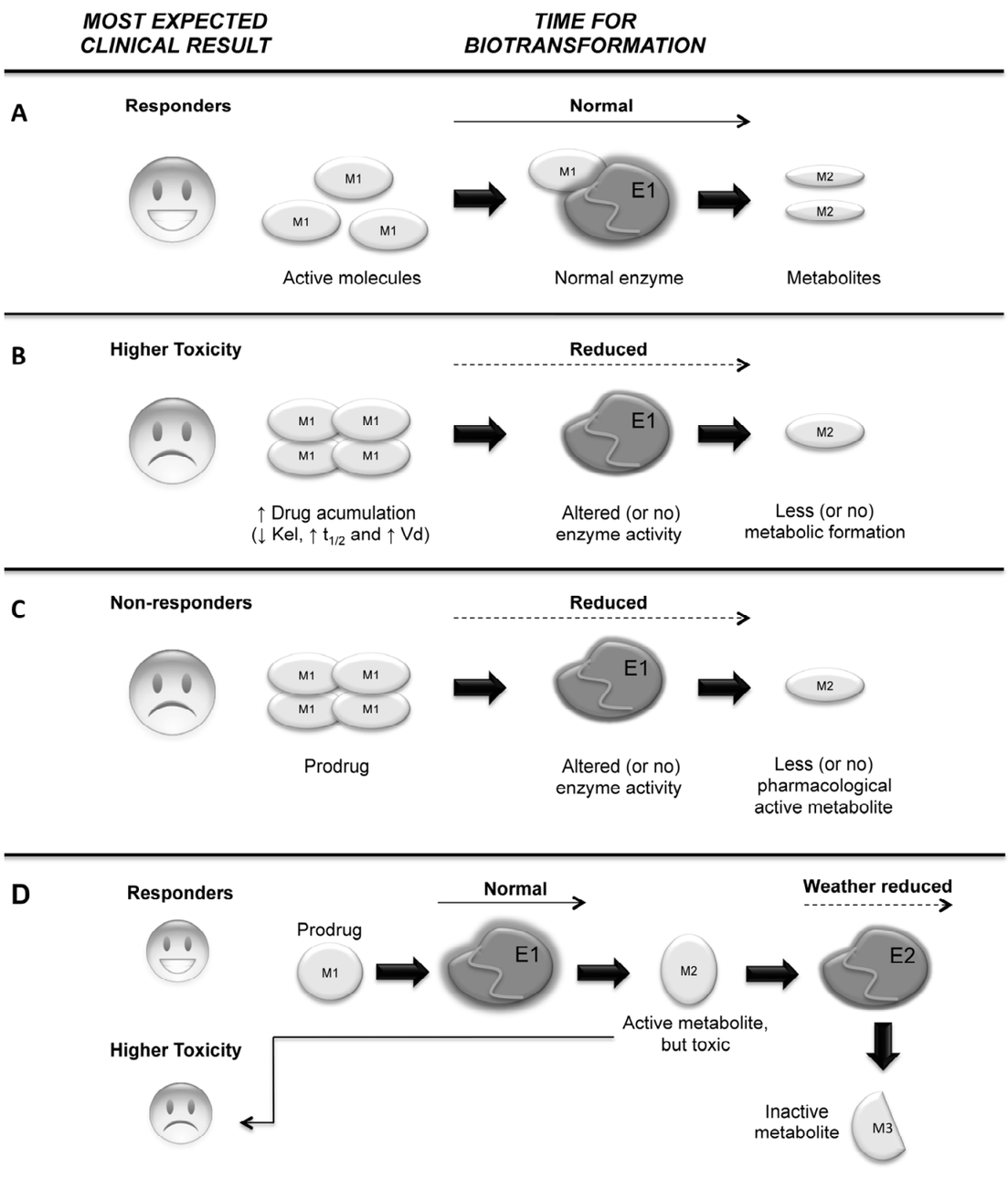

Fig. 1. Overview of the expected clinical result and its relation with activity of drug metabolizing enzymes. M1: pharmaceuticals compounds; E1: phase I biotransformation; M2 and M3: metabolites; E2: phase II biotransformation

metabolic step might cause accumulation of the drug and/or its metabolites in the body if the medicine continues to be taken (Figure 1B). As discussed earlier, genetic mutations in coding and noncoding regions may be involved in such inborn altered enzymatic activity (Ingelman-Sundberg 2001). Some relevant examples come from polymorphisms in CYPs (cytochrome P450) genes, which may result in absence of protein synthesis (*2A6*4*, *2D6*5*),

no enzyme activity (*2A6*2*, *2C19*2*, *2C19*3*, *2D6*4*), altered substrate specificity (*2C9*3*), reduced affinity for substrate (*2D6*17*, *3A4*2*), decreased stability (*2D6*10*) or even increased enzyme activity (2D6*2xn) (Tang et al. 2005). It is important to note that such genetically determined enzyme variation may directly interfere in the drug concentration at the target tissue, and though the pharmacological effect may be observed, the risk of toxicity will also be higher in "poor metabolizers" since it might accumulate to possibly harmful levels. Reduction in drug biotransformation, as observed in drug-drug interactions, will also result in altered expected values for the constant of elimination (Ke), half-life of the drug (t½), volume of distribution (Vd), area under the curve (AUC) and others common useful pharmacokinetic parameters used in therapeutic drug monitoring and adjustment. Based on these reasons, PGx approaches may contribute to the enhancement of clinical outcomes by providing a more effective match between patient and drug dose or type, and consequently reducing the probability of an adverse drug reaction.

Since the effect of inherited variation (genotype) on enzymatic activity isresult of changes in DNA sequence (will be discussed in more details later), it is plausible that there are distinct subgroups of subjects who have different metabolic capabilities (**phenotype**). IIndeed, epidemiologic studies have revealed at least two sub-populations of individuals based on drug metabolizing profile, classified as either "rapid", or "slow" metabolizers. Importantly to note that each metabolic group (rapid or slow) has advantages and disadvantages, and potential outcomes have been related to the type of drug studied. For example, administration of a prodrug may have higher therapeutic efficacy in a rapid than in slow metabolizer phenotype, as the metabolization of such drug is necessary to make it active. In addition, drug biotransformation is fundamental to generate an active-molecule (M2) from a less (or not) active form (M1) (Figure 1C). Despite controversies that exist in the literature about the real impact of pharmacogenetics on clinical practice (Padol et al. 2006), studies have reported different therapeutic response in patients treated with proton pump inhibitors (Tanigawara et al. 1999; Furuta et al. 2001; Klotz 2006). These examples illustrate how important PGx is, on a case-by-case basis.

Furthermore, it is evident that PGx approaches cited here are simplified assumptions of metabolism. Actually, many drugs are sequentially metabolized (Figure 1D) by parallel pathways or a broad range of enzymes to other intermediary metabolites. For practical purposes, two main classes of reactions are considered in the biotransformation of drugs. Exclusively for readability, some basic generalities of each phase reactions will be introduced below from a PGx perspective.

3. Lessons from phase I and II reactions

As discussed elsewhere in this book, the "**phase I**" metabolizing enzymes (or "nonsynthetic reactions") can convert drugs in reactive electrophilic metabolites by oxidation, hydrolysis, cyclization, reduction, and decyclization. The major and the most common phase I enzyme involved in drug metabolism are the microsomal cytochrome P450 (CYP) superfamily. CYPs mediate monooxygenase reactions that generate polar metabolites that may be readily excreted in the urine. Major CYP isoforms responsible for biotransformation of drugs include CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP2E1. However, CYP2D6, a member of this family, has been a true landmark in phase I reactions and also a common target of study in PGx.

Following the scientific vision of Evans and Sjöqvist concerning the inheritability of metabolism profile, Alexanderson continued the refining of the pharmacogenetic studies using twin models. Metabolism of some drugs such as nortriptiline (tricyclic antidepressant) were demonstrated to be under genetic control (Alexanderson et al. 1969). Later, Robert Smith (Mahgoub et al. 1977) and Michel Eichelbaum (Eichelbaum et al. 1979) and their co-workers independently attributed variability in debrisoquine/sparteine oxidation to feasible genetic polymorphisms in debrisoquine hydroxylase or sparteine oxidase (now known as CIP2D6, the same metabolizing enzyme of nortriptiline). In these studies, they suggested that at least two phenotypic subpopulations could be distinguished as "poor" and "extensive" metabolizers. This association between genotype and phenotype was explored only almost ten years after, when the gene encoding CYP2D6 was identified (Gonzalez et al. 1988). Nowadays, it is well recognized that *CYP2D6* polymorphisms may result in four phenotypes according to enzyme activity: **poor metabolizers** (PMs); **intermediate metabolizers** (IMs); **extensive metabolizers** (EMs); and **ultrarapid metabolizers** (UMs). The EM phenotype, considered as "reference", is the most frequent in worldwide populations. PMs inherit two deficient *CYP2D6* alleles, which result in a significant slower CYP2D6 metabolism rate (characterized by increase of the plasma drug levels) (Figure 2). Individuals carrying only one defective *CYP2D6* allele are considered IMs, the "functional" phenotype. Since IMs still have some CYP2D6 metabolic activity, pharmacological responses in those patients are considered marginally better than those observed in PM phenotype.

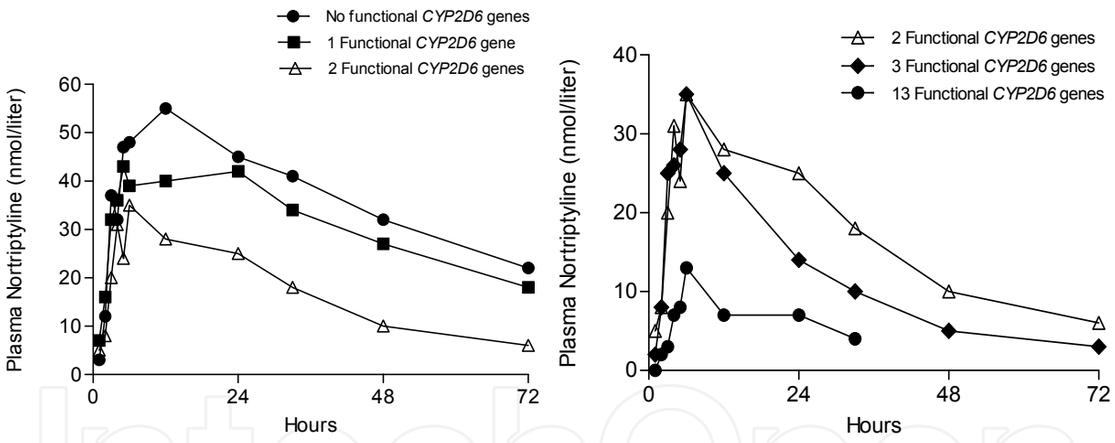

Fig. 2. Effect of functional *CYP2D6* genes in mean plasma concentrations of nortriptyline after a 25-mg oral dose administration. (Dalen et al. 1998).

The UM phenotype results from a gene duplication or even multiduplications. Individuals UMs tend to metabolize drugs at an ultrarapid rate (Ingelman-Sundberg et al. 2007). The relevance of such genetic variation in the biotransformation of drugs is very impressive. First, at least one fifth of all drugs used in clinical practice (or their active metabolites) share a pathway in CYP2D6 route. Among them, include those used to treat heart disease, depression and schizophrenia, for example (Ingelman-Sundberg & Sim 2010; Lohoff & Ferraro 2010). Second, phenotype status directly affects clinical response. Analgesic effects of some prodrugs, such as tramadol, codeine and oxycodone are CYP2D6-dependent, and PMs present low analgesic efficacy (Poulsen et al. 1996; Stamer et al. 2003; Stamer & Stuber 2007; Zwisler et al. 2009). On the other hand, loss of therapeutic efficacy at standard doses

can also be observed in UMs since the drug metabolization occurs at a fast rate (Davis & Homsi 2001). Finally, UM may also present either improved therapeutic efficacy or more frequently severe adverse effects, due to a higher rate of toxic metabolites formation (Kirchheiner et al. 2008; Elkalioubie et al. 2011).

An interesting point is that many chemicals become more toxic (even carcinogenic) only when they are converted to a reactive form by phase 1 enzyme (represented by M2 in Figure 1D). Thus, subsequent biotransformation pathway has a critical role in protecting cells from damage by promoting elimination of such potentially dangerous compounds. In this context, many phase I products are not rapidly eliminated and they may undergo a subsequent reaction, known as **phase II** (represented by E2 in Figure 1D). Phase II reactions are characterized by incorporation of an endogenous substrate (for this reason are called "conjugation reactions") such as glutathione (GSH), sulfate, glycine, or glucuronic acid within specific sites in the target containing mainly carboxyl (-COOH), hydroxyl (-OH), amino (-NH_2), and sulfhydryl (-SH) groups to form a highly polar conjugate (represented by M3 in the figure 1D). As phase I, most phase II reactions generally produces more water-soluble metabolites, increasing the rate of their excretion from the body. However, it is important to notice that the conjugation of reactive compounds by phase 2 metabolizing enzymes will not necessarily convert them into inactive compounds before elimination. Actually, "phase I" and "phase II" terminologies have been more related to a historical classification rather than a biologically based one, since phase II reactions can occur alone, or even precede phase I reactions. In general, more complex routes are involved in drug metabolism though some pathways are preferentially used.

It is worthwhile to mention some clinical considerations with regard to recent advances seen in PGx. First, although genotyping may be useful in predicting a drug response or toxicological risk, classical factors related with variability in drug response (age, organic status, patient compliance and others) must also be considered at every stage of the therapeutic individualization (Vetti et al. 2010). Second, it is widely accepted that genetic variability in DMEs are also directly correlated with susceptibility to unexpected outcomes, such as suicide (Penas-Lledo et al. 2011), cancer (Di Pietro et al. 2010) and other complex diseases (Ma et al. 2011). In others words, PGx approaches are not limited to drug response.

Knowledge of the relevance of phase II enzymes for PGx precedes the CYP2D6 findings. The final touch of this association was done by Price Evans in an elegant and well-designed research on the Finish in 1950`s (Evans et al. 1960). Although his studies about variation of isoniazid metabolism had more impact on public health, Evans advanced the ideas of Hughes and McCusick about the influence of Mendelian inheritance on drug metabolism. In this regard, his findings allowed introduction of the 'fast' and 'slow' metabolizers nomenclature, and which finally provided evidences that genetic variation in drug metabolism could be shown using random families. Subsequent studies demonstrated that the common trimodal profile in plasma isoniazid levels as a result of genetically determined forms of hepatic **N-acetyltransferase (NAT)**. Particularly NAT2 (EC 2.3.1.5), catalyzes not only N-acetylation, but following N-hydroxylation also catalyzes subsequent O-acetylation and N,O-acetylation. NAT2 is a crucial enzyme to convert some environmental carcinogens such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines (AAs), heterocyclic amines (HAs) and nitrosamines (NAs) in more water-soluble metabolite, avoiding accumulation of potentially dangerous metabolites (Hein et al. 2000).

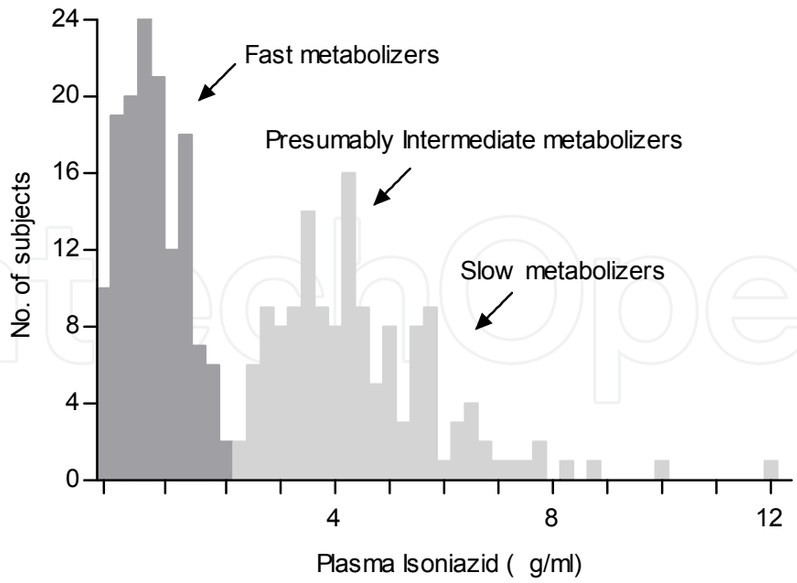

Fig. 3. Polymodal distribution of plasmatic concentrations after an oral dose of isoniazid in 267 subjects (Price-Evans 1962).

Other important phase II enzymes are **Glutathione S-transferases** (**GSTs**; EC 2.5.1.18), which constitute a superfamily of ubiquitous and multifunctional enzymes. As NAT2, GSTs play a key role in cellular detoxification, protecting macromolecules from attack by reactive electrophiles, including environmental carcinogens, reactive oxygen species and chemotherapeutic agents (Ginsberg et al. 2009). One common feature of all GSTs is their ability to catalyze the nucleophilic addition of the tripeptide glutathione (GSH; γ-Glu-Cys-Gly) to a wide variety of exogenous and endogenous chemicals with electrophilic functional groups, thereby neutralizing such sites, and similar with NAT2, rendering the products more water-soluble, facilitating their elimination from the cell. Besides NATs and GSTs, other enzymes are also important in phase II metabolism, such as UDP-glucuronosyl transferases (UGTs), sulfotransferases (SULTs), methyltransferases (as TPMT) and acyltransferases (as GNPAT).

Assumptions between functional variability in DMEs and heritable genetic polymorphisms have allowed recent studies to evaluate, for example, why exposition to a particular toxic substance does not result in the same degree of risk for all individuals. This approach called **toxicogenetics** is considered another arm of PGx. Additionally, toxicological perspectives provide opportunities to evaluate the interindividual variability in susceptibility to a number of disorders such as cancer (Orphanides & Kimber 2003; Di Pietro et al. 2010). As discussed later, it is inevitable that this knowledge would bring out endless debates about ethical questions.

4. Genetic variability in drug response

At this point, it is clear that variability in drug response depends on the complex interplay between multiple factors (including age, organ function, concomitant therapy, drug interactions, and the nature of the disease) and genetic background. Now, we will focus on

the basic principles of genetics to get a better understanding of key issues addressed in PGx, and how genotype data may be used to infer phenotypic designations.

DNA sequence variations that are common in the population (present at frequencies of 1% or higher) are known as polymorphisms (not just "mutations") and they influence the function of their encoded protein, consequently altering human phenotypes. Among such genetic variations, there are at least two common polymorphisms having a substantial influence on the interindividual variation in human metabolism: Single Nucleotide Polymorphisms (**SNPs**) and insertions/deletions (**indels**). SNPs are polymorphisms that occur when a single nucleotide (A, T, C, or G) is altered in the genome sequence. They are largely distributed and account for most variations found in the genome. However, those that occur in genes and surrounding regions of the genome controlling gene expression are notoriously related to susceptibility to diseases or have a direct effect on drug metabolism. SNPs are classified as **nonsynonymous** (or missense) if the base pair change results in an amino acid substitution, or **synonymous** (or sense) if the base pair substitution within a codon does not alter the encoded amino acid. In comparison to base pair substitutions, indels are much less frequent in the genome, especially in coding regions. Most indels within exons (representative nucleotide sequences that code for mature RNA), may cause a frame shift in the translated protein and thereby changing protein structure or function, or result in an early stop codon, which makes an unstable or nonfunctional protein. Important to state that the functional effects of structural genomic variants are not limited by SNPs and indels, but also related to others process such as inversion and multiple copies of genes (as observed in *CYP2D6*), and even the occurrence of a new gene-fusion products.

As presented earlier, population studies have shown the frequency of an appropriate measure of *in vivo* enzyme activity frequently bimodal (with two phenotypes generally termed rapid and slow metabolizers). However, as observed in *CYP2D6* gene, additional phenotypes such as the ultrarapid (those with markedly enhanced activity) or intermediate metabolizers can be detected, resulting in subsets of individuals who differ from the majority (polymodal). As this phenotypic distribution is determined by genetic polymorphisms, the knowledge of alleles variants in selected genes may provide a basis for understanding and predicting individual differences in drug response. Here, we selected the *NAT2* gene, a clinically relevant gene example, to illustrate how PGx data may provide molecular diagnostic methods to improve drug therapy.

4.1 NAT2: Genetic determinants to a range of phenotypes

The gene coding for *NAT2* is located within 170 kb mapped to the short arm of human chromosome 8p22. *NAT2* codifies a 290 amino acid product from the intronless 870 base pair open reading frame (Blum et al. 1990). Numerous allelic variants have been described for *NAT2*. Although the SNPs in the coding exon causing amino acid changes remain most investigated, recent studies have described some *NAT2* SNPs that do not change amino acid codon but may have functional consequences in transcript stability and splicing. *NAT2* SNPs are described in detail on the website http://louisville.edu/medschool /pharmacology/consensus-human-arylamine-n-acetyltransferase-gene-nomenclature).

A number of studies have attempted to relate *NAT2* SNPs to interindividual differences in response to drugs or in disease susceptibility, however some inconsistencies were observed.

A reasonable explanation for this contradictions is that genotyping of individuals SNPs alone may not always provide enough information to reach these goals at genes containing multiple SNPs in high linkage disequilibrium such as *NAT2* (Sabbagh & Darlu 2005). Therefore, it seems more desirable that various combinations of *NAT2* SNPs, known as **haplotypes**, rather than individual SNPs can be required to infer phenotypes of NAT2 acetylation in a trimodal distribution of rapid, intermediate and slow (Vatsis et al. 1995). Thus, genetic alterations in *NAT2* described so far stem primarily from various haplotypes of 20 nonsynonymous (*C29T*, *G152T*, *G191A*, *T341C*, *G364A*, *C403G*, *A411T*, *A434C*, *A472C*, *G499A*, *A518G*, *C578T*, *G590A*, *G609T*, *T622C*, *C638T*, *A803G*, *G838A*, *A845C*, and *G857A*) and seven synonymous SNPs (*T111C*, *C228T*, *C282T*, *C345T*, *C481T*, *A600G* and *C759T*) in the *NAT2* coding exon.

Metabolic phenotyping assays are generally more time-consuming, more expensive, and not suitable in many situations. In this regard, many studies have successfully shown that phenotype prediction of NAT2 activity from genotype data is useful and accurate. However, this requires that all relevant SNPs and/or alleles be analyzed in the population studied since inference of NAT2 phenotypes is assigned based on co-dominant expression of rapid and slow acetylator *NAT2* SNPs, as previously shown (Xu et al. 2002). For example, individuals that have one or more slow acetylator *NAT2* SNPs such as *A191G*, *T341C*, *G590A* or *G857A* are deduced as slow acetylators since these substitutions are diagnostic for defective NAT2 function. However, if at least one rapid *NAT2* SNP is also present, an intermediate acetylator is observed. Failure to detect this hypothetical rapid SNP may explain, in part, an unreliable enzymatic prediction or even unexpected clinical outcomes. On the other hand, there is still no consensus about the number of *NAT2* SNPs considered necessary to infer accurately the human acetylator status. Many studies have performed genotyping using 4 SNPs (*A191G*, *C341T*, *A590G* and *A857G*), but some authors demonstrated that analysis at least of seven SNPs (adding *C282T*, *C481T* and *A803G*) seems more accurate to infer the NAT2 acetylator phenotypes (Deitz et al. 2004). It is important to note that this accuracy may vary depending on the ancestral background of the population under study because the SNP prevalence differs among ethnic groups. For example, our research group found that *G590A*, common to the *NAT2*6* slow haplotype, is present in almost all Afro-Brazilians and Caucasians, but present only in half of Amerindians (Talbot et al. 2010). In fact, even the reference haplotype considered "wild-type" is not common in all ethnic groups. The most common and clinically relevant *NAT2* haplotypes that have been the subject of most studies in recent years are illustrated in Table 1.

4.2 Why computational approach is valuable to infer haplotypes?

Haplotype approaches combining the information of adjacent SNPs into composite multilocus are more informative, robust and valuable in the study of human traits than single-locus analyses. However, problems may occur when *NAT2* SNPs are assigned to a particular combination of two multilocus haplotypes because most *NAT2* SNPs are found in high **linkage disequilibrium** and haplotype assembly from available genotype data which may a challenging task. In other words, the gametic phase of haplotypes is inherently ambiguous when individuals are heterozygous at more than one locus (Figure 4).

Haplotype	SNP and rs identifiers	Amino-acid change	Acetylator phenotype
NAT2*4	**Reference**	**Reference**	**High**
NAT2*5A	**T341C (rs1801280)** C481T (rs1799929)	**I114T** L161L	Slow
NAT2*5B	**T341C (rs1801280)** C481T (rs1799929) **A803G (rs1208)**	**I114T** L161L **K268R**	Slow
NAT2*5C	**T341C (rs1801280)** **A803G (rs1208)**	**I114T** **K268R**	Slow
NAT2*6A	C282T (rs1041983) **G590A (rs1799930)**	Y94Y **R197Q**	Slow
NAT2*6B	**G590A (rs1799930)**	**R197Q**	Slow
NAT2*7A	**G857A (rs1799931)**	**G286E**	Slow*
NAT2*7B	**G857A (rs1799931)** C282T (rs1041983)	**G286E** Y94Y	Slow
NAT2*12A	**A803G (rs1208)**	**K268R**	Rapid
NAT2*12B	**A803G (rs1208)** C282T (rs1041983)	**K268R** Y94Y	Rapid
NAT2*12C	**A803G (rs1208)** C481T (rs1799929)	**K268R** L161L	Rapid
NAT2*13A	C282T (rs1041983)	Y94Y	Rapid
NAT2*14A	**G191A (rs1801279)**	**R64Q**	Slow
NAT2*14B	**G191A (rs1801279)** C282T (rs1041983)	**R64Q** Y94Y	Slow

Common non-synonymous nucleotide and amino-acid change are bolded.
*Substrate dependent.

Table 1. Common studied *NAT2* haplotypes and associated acetylator phenotype.

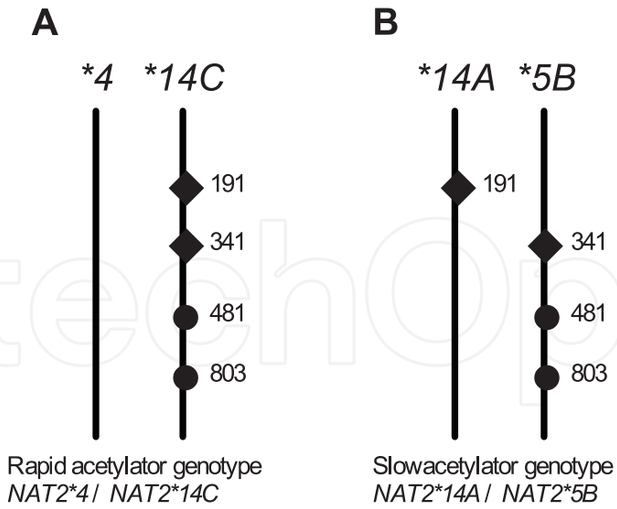

Fig. 4. Haplotype classification is depend on gametic phase and may induce equivocally phenotype. Subject can be either rapid (A) or slow (B) acetylator depending on whether these mutations are located in the same or different chromosome.

As current routine genotyping and sequencing methods typically provide unordered allele pairs for each marker, *NAT2* haplotypes must be determined by inferring the phase of the alleles in order to assign an acetylator phenotype to a particular individual. **Haplotype Phase Inference** is based on transfer of ordered genotypes to all members in the pedigree at all loci, consistent with all observed genotype data and Mendelian segregation (readers may refer to an article by Slatkin 2008 for more details). In this regard, statistical and computational methods for haplotype construction from genotype data of random individuals received considerable attention due to several approaches have been developed to infer the true haplotype phase (Stephens & Donnelly 2003; Scheet & Stephens 2006). For example, there is a web server that implements a supervised pattern recognition approach to infer NAT2 acetylator phenotype (slow, intermediate or rapid) directly from the observed combinations of 6 *NAT2* SNPs (Kuznetsov et al. 2009). Although haplotype data may also be obtained in family studies and experimentally from general population, these methods are considered laborious and expensive.

4.3 From genetic alterations to protein function: Moving from pharmacogenetics to pharmacogenomics

Given that genetic alteration may influence a protein function, several studies were conducted to assess how polymorphisms in genes of the corresponding DME can modify drug efficacy/toxicity and disease risk. In general, results have been obtained in epidemiologic or clinical studies and for better understanding of the population's PGx. Consequently, in order to investigate these associations, both *in vitro* and *in vivo* studies using a variety of substrates have been performed to assign phenotypes to many identified genotypes.

Functional studies and intracellular tracking of polymorphic variants are contributing to appreciation of how individual mutations modify protein function. In general, these studies

support the idea that different combinations of polymorphisms in the gene coding region result in proteins with altered stability, degradation, and/or kinetic characteristics. For example, slow acetylator *NAT2* alleles showed reduced levels of NAT2 protein when compared with reference *NAT2*4* allele, and possible mechanisms SNP-induced protein alteration are discussed elsewhere (Zang et al. 2007). Moreover, reductions in catalytic activity for the N-acetylation of sulfamethazine and 2-aminofluorene, a sulfonamide drug and an aromatic amine carcinogen respectively, were observed in *NAT2* alleles possessing *G191A*, *T341C*, *A434C*, *G590A*, *A845C* or *G857A* (Fretland et al. 2001). As many chemicals cannot be tested *in vivo*, including certain human carcinogens, physiological effects of genetic alterations as SNPs and haplotypes, have been investigated *in vitro* in recombinant expression systems to determine the corresponding phenotypes.

The effects of genetic alteration on proteins are the basis for bimodal or polymodal phenotypes. With these relations between genotype and phenotype recognized, studies have shown promising pathways supposed to be susceptibility molecular targets for a number of drug side effects and certain malignancies predisposed by DME genes polymorphisms.

Furthermore, the molecular homology modeling techniques, including SNP locations and computational docking of substrates, have increased the understanding of the protein structure-function relationship. In this context, PGx has been a universal discipline providing many of the driving forces behind of the scientific development of the human genetics, pharmacology, clinical medicine and epidemiology. Additional evidences from laboratory-based experiments, haplotype mapping and clinical tests, lead us to believe that PGx will be a major contributor in the preventive and curative modern medicine.

5. Clinical pharmacogenetics and potential applications

Individual variability in plasma drug levels has been considered by many studies as a primary cause of therapeutic inefficacy and pharmacologic toxicity. Thus, matching patients to the drugs and dose that are most likely to be effective (maximizing drug efficacy) and least likely to cause harm (enhancing drug safety) is the main purpose of the novel contributions PGx.

Clinically relevant examples of inherited variation that may influence the individual's drug-metabolizing capacity and consequently pharmacokinetic properties of a drug are available in the literature. One of the earliest pharmacogenetic tests resulting in clinically important side effects was on the enzyme **thiopurine methyltransferase (TPMT)** (Krynetski et al. 1996). TPMT metabolizes two thiopurine drugs: azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP), used in the treatment of autoimmune diseases and acute lymphoblastic leukemia. Polymorphism in *TPMT* gene causes some individuals to be particularly deficient in TPMT activity, and then thiopurine metabolism must proceed by other pathways, one of which leads to cytotoxic 6-thioguanine nucleotide analogues. This metabolite can lead to bone marrow toxicity and myelosuppression. Such genetic variation in TPMT affects a small proportion of people (approximately 0.3% of the population), though seriously. As empiric dose-adjustments of AZA and 6-MP is risky, *TPMT* genotyping before institution pharmacotherapy by identifying individuals with low or absent TPMT enzyme

activity may provide useful tools for optimizing therapeutic response and prevent toxicity (myelosuppression) (Krynetski & Evans 2003). In addition, *TPMT* genotype and drug adjustment may reduce the risk of secondary malignancies, including brain tumors and acute myelogenous leukemia (McLeod et al. 2000; Stanulla et al. 2005).

NAT2 pharmacogenetics has attracted significant attention as N-acetylation polymorphism seems to predispose to an increased risk of drug-induced hepatotoxicity in patients administered **isoniazid** for the treatment of tuberculosis. Although exact mechanism of isoniazid-induced hepatotoxicity is unknown, recent studies have provided exciting results. Until recently, findings have proposed that metabolite responsible for isoniazid-induced hepatotoxicity was acetylhydrazine (AcHZ) which can undergo further metabolism by CYPs to toxic reactive acetyl free radicals in patients with slow NAT2 acetylation capacities (figure 5). These toxic metabolites can form covalent bonds with liver cell macromolecules, interfering with their function and hepatocellular necrosis. In addition to this reason, some studies have also suggested that patients carrying both slow acetylator NAT2 and fast CYP2E1 isoforms may have a severe exacerbation outcome. Furthermore, it is believed that hydrazine (Hz) is also responsible for the isoniazid-induced hepatotoxicity based on results that metabolic activation of Hz causes hepatic disorder. Also in this second proposition, slow acetylators may be injured since Hz is metabolized by NAT2 to the less toxic derivative diacetylhydrazine (DiAcHZ), which is then excreted in the urine. On the other hand, fast acetylation of AcHZ and Hz in NAT2 rapid acetylators should theoretically form DiAcHZ efficiently and therefore reducing the oxidative metabolites accumulation from AcHZ. In fact, several studies found an increased risk in slow versus fast acetylators through genetically determined phenotype (Higuchi et al. 2007). However, there are conflicting data on whether *CYP2E1* genotypes do or do not increase the risk of isoniazid-induced (Cho et al. 2007).

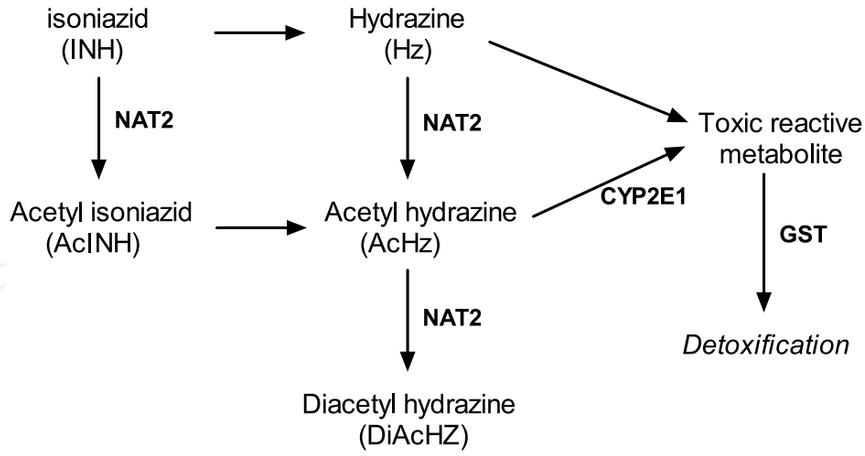

Fig. 5. Major enzymes involved in isoniazid biotransformation and relevant metabolites.

Isoniazid metabolic pathways clearly exemplify that elimination of most drugs involves the participation of several families of drug metabolizing enzymes. Therefore, it is incoherent thought that one or few isolated host factors that only response to drugs. However, there are few studies focusing on the relationship between the genotypes of related enzymes and susceptibility to drug adverse reactions. As shown in Figure 5, is theoretically possible that GST isoforms, which are genetically determined to a great extent, may also influence INH

metabolism. In this way, a study found that well known *GSTM1* null genotype influenced the serum concentration of Hz in the NAT2 slow acetylators independently of their CYP2E1 phenotype (Fukino et al. 2008). Thus, more efforts are necessary to uncover the important question: interactions between *NAT*2 and *CYP2E1* phenotypes, in addition to the GSTs, may have potential risks for isoniazid-induced hepatotoxicity? Thus, as a general rule, a better understanding of genetic factors in a more studies manner will be useful to demonstrate that prediction of toxicity is possible and consistently reliable.

In addition to significant number of publications available in the scientific literature, others comprehensive, public online resources are also available for beginners and experts in PGx. Undoubtedly, one of the most important is **Pharmacogenomics Knowledge Base** (**PharmGKB**, http://www.pharmgkb.org). The reader will find up-to-date information about the most important genes involved in drug response, highlighted summaries, pathway diagrams, and accurate literature (Sangkuhl et al. 2008). In general, the ultimate goal of such services is to guide appropriate PGx knowledge. Common data collected (with few modifications) from PharmGKB in regard to PGx polymorphisms of phase I DMEs and clinical associations are summarized in Table 2. Since we discussed earlier about PGx of *CYP2D6*, we purposely excluded it this table.

Gene	Common Alleles/Effect	Common substrates	Clinical evidences	References
CYP2A6	**2* (L160H) **5* (G479V) **7* (I471T) **11* (S224P) **12* (10 aa substitutions) **17* (V365M) **18* (Y392F) **20* (196 frameshift)	Coumarin, SM-12502, Tegafur#, Nicotine and 5-Fluorouracil	Influence on nicotine adverse effects and variability in quit smoking	(Malaiyandi et al. 2006; Ozaki et al. 2006; Ho et al. 2008)
			Altered therapeutic responses to antineoplastic Tegafur	(Daigo et al. 2002; Kong et al. 2009)
CYP2B6	**2* (R22C) **4* (K262R) **5* (R487C) **6* (Q172H; K262R)	Tamoxifen, Clopidogrel#, Carbamazepine#, Cyclophosphamide, Nicotine and Diazepan	Efavirenz effect and central nervous system side effects	(Haas et al. 2004; Ribaudo et al. 2010)
			Sub-therapeutic plasma concentrations of efavirenz	(Rodriguez-Novoa et al. 2005; ter Heine et al. 2008)
			Benefits of efavirenz dose adjustment	(Gatanaga et al. 2007; ter Heine et al. 2008)

Gene	Common Alleles/Effect	Common substrates	Clinical evidences	References
CYP2C9	*2* (R144C) *3* (I359L) *5* (D360E) *6* (273 frameshift) *13* (L90P)	Warfarin, Phenytoin, Tolbutamide, Glibenclamide, Gliclazide, Fluvastatin, Losartan, Ritonavir and Tipranavir.	Variability in warfarin therapy and elevated risk of severe bleeding	(Aithal et al. 1999; Takahashi et al. 2006; Gan et al. 2011)
			Elevated risk of hypoglycemia attacks during oral antidiabetic treatment.	(Kidd et al. 1999; Tan et al. 2010; Gokalp et al. 2011)
			More frequent symptoms of overdose in phenytoin therapy	(Ninomiya et al. 2000; van der Weide et al. 2001; Kesavan et al. 2010)
CYP2C19	*2A* (splic; I331V) *2B* (splic; E92D) *2C* (splic; A161P; I331V) *3A* (W212X; I331V) *3B* (W212X; D360N; I331V) *9* (R144H; I331V) *17* (I331V)	Mephenytoin, Lansoprazole, Omeprazole, Selegiline, Imipramine, Fluoxetine Diazepan, Phenobarbital and Proguanil	Inadequate response to clopidogrel* and higher rate of major adverse cardiovascular events (thrombosis)	(Mega et al. 2009; Mega et al. 2010; Kelly et al. 2011)
			Increased risk of proguanil treatment failures	(Kaneko et al. 1997)
			Differences in clinical efficacy of proton pump inhibitors.	(Zhao et al. 2008; Furuta et al. 2009; Sheng et al. 2010; Yang & Lin 2010)
			Nelfinavir pharmacokinetics and virologic response in HIV-1-infection.	(Saitoh et al. 2010)

#prodrugs; aa: amino acid; splic: splicing defect. More information about allele, protein, nucleotide changes, trivial name and effect of the gene of polymorphism on enzyme activity may be found in http://www.cypalleles.ki.se/index.htm and http://www.snpedia.com/index.php/SNPedia.

Table 2. Common alleles, substrates and clinical evidences of some CYPs.

6. Ethnic characterization is not sufficient to reach pharmacogenetic goals: Focus on personal genomics

Inherited determinants generally remain stable throughout a person's lifetime (unlike other factors influencing drug response), making the pharmacogenetics approach attractive. However, both interethnic and intraethnic variability for a specific allele in human populations are extremely large and may have relevant clinical implications. *NAT2* is a good example of such gene. Several *NAT2* SNPs causing defective enzymes are heterogeneity distributed in the world making 50% of Caucasians but only 10% of Japanese slow acetylators, for example. Moreover, our research group demonstrated that some discrepancies in allelic frequencies in an important DME, even within the same population. (Magno et al. 2009).

Undoubtedly, PGx variability explains in part why there are important differences in response to conventional drug-based therapies among different ethnic groups. But, from a biological standpoint, what are the probability to predict efficiently and accurately an individual response to drug from a multi-ethnic study? Low, at least. Several evidences have provided enough data to concern about it. Attempts to predict genotypes and phenotypes from ethnic perspectives have been become less meaningful, mainly in parts of the world in which people from different regions have mixed extensively. Thus, recent studies have pointed out that ethnicity not always serves as a start point to define drug regimes because it typically not emphasizes biological components. To group individuals in only a same category based in non-biological criteria, is to assume that people from these groups have same biological backgrounds. For example, clinical and pharmacological trials have traditionally considered the different geographical regions of Brazil as being very heterogeneous. However, a recent study found that the genomic ancestry of subjects from these different regions of Brazil is more homogeneous than anticipated (Pena et al. 2011). In the same way, individual categorization depends not on physical appearance of the subjects (Parra et al. 2003).

Therefore, it is evident that results from population studies could be useful in some situations, but the fact that subjects have their own variations reinforce the necessity to study an individual's genetic profile and not ethnic populations.

7. Are PGx approaches cost-effective?

Unquestionably, some success has been achieved in recent years in establishing the clinical utility of the pharmacogenetic testing. However, it remains questionable whether it is cost-effective or not. To justify routine testing, PGx technology must be more practical than the available approaches and involve a clinical benefit higher than those reported and sufficiently to cover expenditures in genetic testing. Unfortunately, data on cost-effectiveness of PGx are currently limited and have been the subject of controversy in the literature. A possible explanation is that therapeutic outcomes depend on many poorly defined factors other than pharmacogenetic variation, such as the cost of therapeutic failure and circumstances surrounding patient therapy. Furthermore, to address the issue of "effectiveness" is difficult, considering that PGx purposes not only attempt save time and money, but also avoids any unnecessary physical suffering and emotional traumas.

In general, studies have shown that PGx is potentially cost-effective under certain circumstances (Carlson et al. 2009; Vegter et al. 2009; Meckley et al. 2010). Some authors consider that findings showing non-robust benefit of PGx testing are due to limited knowledge of its therapeutic application since access to technology and genotyping expenses are no longer limiting factors. Influence of *CYP2D6* alleles on therapeutic efficacy of psychiatry drugs clearly illustrates this. Besides the influence of *CYP2D6* alleles on metabolism of most antipsychotics drugs, studies investigating the association between *CYP2D6* genotypes and antipsychotic response have reported no predicted clinical improvement (Zhang & Malhotra 2011). Probably, this enzyme only has a significant clinical impact on a smaller non-investigated subgroup of drugs. In fact, a genetic variation that merely affects the drug elimination, modestly increase the frequency of an adverse effect or a common side effect that is well tolerated may still not be of sufficient importance to justify pharmacogenetic testing.

Presumably, cost-effectiveness of PGx also can vary from high to low depending on the illness and gene involved. According to this proposition, important support of the cost-effectiveness of PGx comes from clinical situations where PGx variations have major impact on therapeutic outcomes and clinical cost. Genotyping of *TPMT* before starting azathioprine treatment (Hagaman et al. 2010), *HTR2A* (serotonin 2A receptor) in selective serotonin reuptake inhibitors therapy (Perlis et al. 2009) and *CYP2C9* plus *VKORC1* (vitamin K epoxide reductase complex subunit 1) before warfarin treatment (Leey et al. 2009; You 2011) are well-known examples.

Important to date that economic evaluations of PGx have all highlighted the need to improve the quality of the evidence-based economics (Payne & Shabaruddin 2010), since a number of studies have been inconclusive (Verhoef et al. 2010). Finally, it is possible that the rapidly decreasing cost of genetic analysis and knowledge of the therapeutic application of PGx will be able systematically to make PGx approaches more and more cost-effective technology.

8. Ethics in PGx and final considerations

Past lessons had enabled us to see the rising of personalized prescriptions in improving prevention of serious adverse drug reactions, therapeutic effect and patient compliance. However, they have not resolved the ethical issues that are emerging in PGx research. Although the barriers between technological advances and the view of human well-being are not so clear-cut, both perspectives will be discussed below.

The first issue comes from the source of PGx data: human samples. Samples and data collected as a part of the research are stored and offer robust information about genome, cells, biological functions, life-style, previous diseases, and many others. Although it seems like a conspirator theory or just an ideological issue, because historical facts unfortunately have failed to clearly show this fact. A businessman from Seattle called John Moore developed hairy cell leukemia and was treated by a highly qualified team from a notorious research center of an American University. Then, Moore returned to the center in order monitor his condition seven years later, fearing a recurrence of the leukaemia. However, he was shocked to learn that besides his physician's preoccupation about his health, there indeed was another interest at stake. And that was a million dollar contract that was already

negotiated and signed, to develop a cell line from Moore blood sample (now known as "Mo-cell line") without Moore's consent. It became a court case. Surprisingly, California Supreme Court decided the case in favour of the physician. This landline decision gave a clear impetus to commercialization of samples from human and led to patents developed from human samples. After that, new patents based on human samples gave a new gold rush treasure. It is obvious that the chapter's purpose is not to go deeper in this kind of philosophical issues, but the reader must think about the real impact of what the informed consent really represent and what should guide its free applications. Moreover, many studies involving thousands of individuals with application of "reconsents" and "tiered consent" aiming to obtain specimens to future research will also new clinical directives in PGx research.

A second bioethical hallmark allow the subject or patient confidentiality. How, for whom and why will the information be accessed? As a part of clinical diagnosis, it seems more reasonable that the patients themselves have special interest and the confidentiality is not different as in the case of other diseases. However, could patients' relatives know about inherited disorders or increased disease risk? Could employers and health insurances companies have access to this genetic information? For instance, we may suppose a company looking for employees based on the "tolerance levels" to exposure of occupational toxicants. In this regard, studies have shown a wide range of carcinogenic toxicants such as arsenic (Hernandez et al. 2008; Paiva et al. 2010), benzene (Sapienza et al. 2007) and polycyclic aromatic hydrocarbons (Rihs et al. 2005) in which detoxification is genetically influenced. Thus, should this information be used for admission or even resignation? Defenders of the breaking of genomic confidentiality usually have highlighted the cost-benefit of "protecting his/her own health", but some health insurance companies may use these data to introduce different fares depending on individual susceptibility such as "high costs" for subjects defined as "higher disease risk", for example. Actually there is no novelty on that since many worldwide apply different rates for automobiles or health insurance based on age, gender, life-style, previous disease and some others. In fact, companies, regulatory and public funding agencies are discussing how to integrate PGx practice into public health care (Robertson et al. 2002; Evans 2010).

Examples above illustrated lead to a third reflection: Equity. As discussed by Peterson-Iyer, "market forces do not guarantee justice in the distribution of health care". In a different way of the "one-size-fits-all" (a blind approach for drug prescription with regard to their pharmacokinetic profile), PGx approaches improving drug safety and efficacy are already beginning to be performed only in some private and medical centers. It is unquestionable that in short time clinical practice of PGx will favor highly sophisticated higher one's economic status. If currently there are a significant numbers of subjects uninsured for basic health care, would PGx rectify or exacerbate the profoundly disturbing those with higher economic status inequalities in the health care system? (Peterson-Iyer 2008). Indeed many other bioethical questions might be relevant, which we may not be able to treat here. We encourage the readers to read further on this subject from various excellent articles on these issues (Williams-Jones & Corrigan 2003; Weijer & Miller 2004; Patowary 2005; Sillon et al. 2008; Howard et al. 2011).

In conclusion, unequivocally DMEs still remain helping to elucidate the well-known mechanisms of variability in drug response and have been the major contributor in the successful advances in PGx (Freund et al. 2004; Jaquenoud Sirot et al. 2006; Swierkot &

Slezak 2011). Past lessons have taught us to consider each individual as a unique person from metabolic perspective. Currently, PGx is leading us to uncover several and potential applications of PGx in the clinical practice, which involves an interconnected puzzle pieces with patients, health professionals, industry and governmental regulatory agencies. Finally, PGx starts to tell us that all its benefits should also be applied in a close future for all members of the society and though differences in our DNA, pharmacogeneticians always worked together in the same perspective to improve the health of people without distinction.

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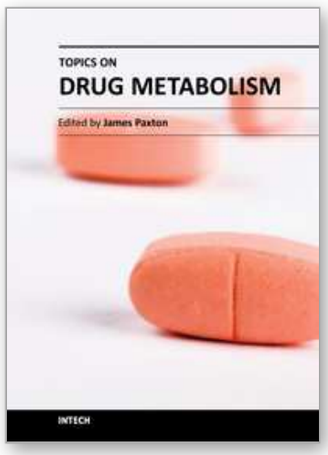

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In order to avoid late-stage drug failure due to factors such as undesirable metabolic instability, toxic metabolites, drug-drug interactions, and polymorphic metabolism, an enormous amount of effort has been expended by both the pharmaceutical industry and academia towards developing more powerful techniques and screening assays to identify the metabolic profiles and enzymes involved in drug metabolism. This book presents some in-depth reviews of selected topics in drug metabolism. Among the key topics covered are: the interplay between drug transport and metabolism in oral bioavailability; the influence of genetic and epigenetic factors on drug metabolism; impact of disease on transport and metabolism; and the use of novel microdosing techniques and novel LC/MS and genomic technologies to predict the metabolic parameters and profiles of potential new drug candidates.

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