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Forensic Pharmacogenetics

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1. Introduction

Pharmacogenetics and *pharmacogenomics* are gaining importance both in the clinical setting and in forensic pathology to investigate causes of death where no findings emerge from autopsy, and in the medical liability arena where scientific issues meet the justice system (Pilgrim et al., 2011). Generally speaking, *Pharmacogenetics* is the study of how genetic variations give rise to differences in drug response, while *pharmacogenomics* (PGx) is the application of genomic technologies to the discovery of new therapeutic targets (Evans & Relling, 1999). Nevertheless, there is a diversity of opinion regarding the definitions and benefits of pharmacogenetics and pharmacogenomics. Depending on the purpose, pharmacogenetics can be used to define applications of single gene sequences or a limited set of multiple gene sequences, but not gene expression or genome-wide scans, to study variations in DNA sequences related to drug action and disposition. Pharmacogenomics can be used to define applications of genome-wide single-nucleotide polymorphism (SNP) scans and genome-wide gene expression analyses to study variations influencing drug action (Lesko et al., 2003). Some authors use a very broad definition of pharmacogenomics including the study of inter-individual variations in whole-genome or candidate gene single nucleotide polymorphisms (SNP maps), haplotype markers and alterations in gene expression or inactivation that might be correlated with pharmacological function and therapeutic response. Pharmacogenetics is narrower in definition and refers to the study of inter-individual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics), including polymorphic variation in genes encoding transporters, drug-metabolizing enzymes, receptors and other proteins (Lesko & Woodcock, 2004). With the accumulating knowledge of human genomic variation, the Human Genome Project offers the opportunity to develop personalized medicine, decreasing adverse drug reactions and increasing the efficacy of drug treatment (Weinshilboum & Wang, 2004). Historically, Johansson & Ingelman-Sundberg (Johansson & Ingelman-Sundberg, 2011) consider that inter-individual variation in response to a xenobiotic was probably described first by Pythagoras in 510 BC when he noted that some individuals developed hemolytic anemia after ingestion of fava beans. Then, they record that at the beginning of the last century, Garrod and Oxon suggested the involvement of a genetic component in biochemical processes where the cause of inter-individual differences in adverse reactions was because of enzyme deficiencies (Garrod, 1902, as cited in Johansson & Ingelman-Sundberg, 2011). Observations implying that genetic variation was responsible

for the diversity in some drug responses was established nearly 50 years ago, with the discovery that deficiency in glucose-6-phosphate dehydrogenase (G6DP) results in hemolytic anemia following ingestion of the anti-malarial primaquine (Beutler, 1959). Another example is succinylcholine, which is administered as an adjunct to anesthesia and can induce prolonged apnea due to altered kinetics of a pseudocholinesterase (Lehmann & Ryan, 1956). In 1959, Vogel coined the term of pharmacogenetics to describe inherited differences in drug response (Vogel, 1959). The best-known example of a genetic defect in drug biotransformation is the acetylation polymorphism in tuberculosis therapy with Isoniazid characterized by mutations in *N*-acetyltransferase-2 (*NAT2*) on chromosome 8 (Evans et al., 1960). Alvan et al. (Alvan et al., 2001) remember the case of debrisoquine, an antihypertensive agent inducing orthostatic hypotension in a small percentage of individuals. The reason for the exaggerated effect 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, 1977, as cited in Alvan et al, 2001). The enzyme named "debrisoquine hydroxylase" is now known as CYP2D6. The oxidation of sparteine was found to be catalyzed by the same enzyme (Eichelbaum, 1975, 1979 as cited in Alvan et al, 2001). Now it is well-established that the therapeutic failure of drugs, and adverse side-effects in individuals may also have a genetic component due to genetic variations in the receptors, ion channels, transporter, enzymes and regulatory proteins involved in drug metabolism that may influence pharmacodynamics (e.g. the binding and functional capacity of the receptor or regulatory proteins) and pharmacokinetics, consisting in drug bio-availability at the level of metabolic enzymes and transporters. Most studies have focused on single nucleotide polymorphisms (SNPs) in genes encoding important metabolizing enzymes, like the cytochrome P450 enzyme superfamily, revealing an association with clinical phenotypes of drug efficacy/toxicity (Bishop & Ellingrod, 2004; Korkina et al., 2009; Mellen & Herrington, 2005; Wilkinson, 2005; Yang et al., 2010). One of the goals of pharmacogenetics is to develop predictive genetic tests to reduce the risks associated with drug administration (de Leon et al., 2006, 2009). According to the World Health Organization (WHO), adverse drug reactions (ADRs) are any harmful, unintended reactions to medicines that occurs at doses normally prescribed for prophylaxis, diagnosis and therapy and in some cases can lead to death (Edwards & Aronson, 2000). ADRs represent a significant clinical and economic problem: a prospective study conducted in the United Kingdom showed that 6.5% of hospital admissions are related to ADRs (Pirmohamed et al., 2004). According to the Food and Drug Administration (FDA), the frequency of reported serious and fatal adverse drug events increased 2.6 fold from 1998 through 2005 (Moore et al., 2007). Moreover, it has been estimated that ADRs were between the fourth and sixth leading causes of death in the world due to treatment with drugs like anti-inflammatories, analgesics, antidepressants, sedatives, anticoagulants and antibiotics (Carleton et al., 2009; Lazarou et al., 1998). Given the association between response to treatment and genetic variability on the basis of clinical trials, the European Medicines Agency (EMA) and the FDA currently recommend the use of biomarkers in informing prescribing decisions for certain drugs (Frueh et al., 2008). Moreover, growing information is available on biomarkers indicating whether a therapy could work on a particular individual. In 2004, a "Personalized Medicine Coalition" was launched in the USA, giving strong input to the US Senate bill on the Patient-Centered

Outcome Research Act. But questions arise, including: Will pharmacogenetics in general be accepted by physicians and patients? "Safe and effective medicines for all" is a vision that will not come true in general. Furthermore, even if its outcome and cost-effectiveness have to be proven, personalized medicine can currently contribute to solving the problems of lack of efficacy, drug resistance and adverse effects in some indications, and this opportunity should be used (Cascorbi, 2010). The scientific literature highlights the magnitude of this public health problem at different levels and point of views and illustrates the need for improved systems to select the appropriate drug dosage to achieve the optimal therapeutic response, avoid therapeutic failure and minimize side-effects and toxicity (Davies et al., 2009). Recently, Sim et al. (2011) emphasize the need of updated databases for providing guidance to both scientists, physicians, regulatory agencies, and industries to cope with this major problem in human health. The medico-legal implications are evident both for medical liability issues and in forensic death investigation.

2. Genetic polymorphism of Cytochrome P450 (P450 or CYP)

The primary site of drug metabolism is the liver, where enzymes chemically change drug components into substances known as metabolites that are then bound to other substances for excretion mainly through the kidneys, lungs or bodily fluids or by intestinal re-absorption. Some drugs do not change chemical structure and are removed from the body as such. Drug pharmacokinetics and pharmacodynamics are regulated by complex chemical reactions with the participation of numerous proteins encoded by different genes, deputies for the transport and metabolism of drugs, or involved in their mechanism of action (Weinshilboum, 2003). Two different types of metabolic reactions are involved: in *phase 1* molecules are characterized by oxidation, reduction and hydrolysis reactions, in *phase 2* drugs are conjugated with other compounds and then discarded (Johansson & Ingelman-Sundberg, 2011; Zhou et al., 2008). If two or more polymorphic genes regulate drug metabolism and transport inside a cell, the variability in the response to treatment depends on the interaction of these gene variants. The cytochrome P450 enzyme system plays a central role in phase I oxidative metabolism of the vast majority of prescribed drugs and also of endogenous substances (Bertz & Granneman, 1997). The genes coding for these enzymes are called *CYP*. The Human Genome Project identified 57 human *CYP*s divided into families and subfamilies based on structural similarity in amino acid sequence of the enzymes. Enzymes in families 1 to 3 are involved in the detoxification of exogenous chemicals, whereas the remaining groups are mainly active in the metabolism of endogenous compound like steroids, fatty acids and bile acids (Ingelman-Sundberg & Sim, 2010). Many of the genes involved in drug metabolism are highly polymorphic and all researchers specify the different *CYP* variants as reported at the Human *CYP* allele nomenclature web site www.cypallele.ki.se (Oscarson & Ingelman-Sundberg, 2002). Sim et al. (Sim et al, 2011) describe that the main purpose of the *CYP*-allele website is the management of new allele designations based on recognized nomenclature guidelines, facilitation of rapid publication, as well as providing a readily available summary of alleles and their associated effects. In addition they summarize the inclusion criteria of the new alleles in the website: submission of new alleles is achieved by contacting the Webmaster of the *CYP*-allele Website, whereby the data characterizing the allele is reviewed for potential allele name designation. All information is kept confidential and a manuscript in preparation can often serve as a good basis for review and discussion between the author and the Webmaster. Designation of allele names outside the *CYP*-allele nomenclature

committee is not advised, due to the apparent risk of confusion in the literature. Submissions with respect to additional functional in vivo and in vitro characterization of alleles listed are also highly relevant, and aids in keeping the CYP-allele Website up to date.

2.1 P 450 genes family: From genotype to phenotype

Of all the isoforms of the P450 gene family, *CYP2D6*, *CYP2C19*, *CYP3A5*, *CYP2C9*, *CYP2B6*, *CYP2C8*, *CYP2A6* and *CYP1A2* are the most important and polymorphic enzymes and are responsible for several phase I metabolism xenobiotics (Anzenbacher & Anzenbacherová, 2001; Daly, 2003; Ingelman-Sundberg, 2004). In particular, *CYP2D6*, characterized by a high inter-individual variability in catalytic activity mainly caused by genetic polymorphisms, will be described in depth. The genetic bases of the polymorphism are single nucleotide polymorphisms, insertions/deletions and gene copy number variations (Ingelman-Sundberg et al., 1999). Because of such variability, individuals could be classified into four different phenotypes: ultra-rapid metabolizers (UM) with more than two active gene copies on the same allele or increased expression of a single gene, extensive metabolizers (EM) carrying two functional alleles, intermediate metabolizers (IM) with one defective allele or two partially defective alleles, and poor metabolizers (PM) lacking functional enzymes due to defective or deleted genes. PM and UM are the most clinically important phenotypes: PM individuals are at risk of having a higher than expected serum concentration in relation to the drug dose and hence more side-effects, especially in the case of drugs with a narrow therapeutic index (White, 2010; Prandota, 2010). Instead, UMs may require higher doses and more frequent administration of a drug in an active form to achieve optimal therapeutic concentrations. However, when an inactive “pro-drug” must be converted to the active metabolite (e.g. codeine and tamoxifen), the therapy will be ineffective in PM subjects and UMs will metabolize it quickly with accumulation of the metabolite and consequent toxicity. As a result, drug toxicity is related to metabolizer status (Ingelman-Sundberg et al., 1999; van der Weide & Steijns, 1999). Moreover, the phenomenon of *phenocopying* must be taken into account where EM individuals turn into apparent PM or IM phenotypes because of drug-drug interactions (Owen et al., 2009). Many drugs also inhibit or induce the activity of CYPs and knowledge of CYP–drug relations is therefore essential to recognize incompatible drug combinations and allows individualized therapies (Mishra et al., 2010). For this purpose, a user-friendly platform for researchers and health professionals was developed where each drug was attributed to those CYPs involved in drug metabolism as substrate, inhibitor or inducer. The SuperCYP database contains 1170 drugs with more than 3800 interactions including references (Preissner et al., 2010). Nevertheless, epigenetics, defined as heritable phenotypic changes not involving alteration in nuclear DNA, promises answer to interindividual variability in drug response not associated to genetic polymorphism (Ingelman-Sundberg & Gomez, 2010). Indeed, the CYPs expression can be influenced by diet, lifestyle and environmental pollutants. Update of P450 epigenetics knowledge and its relevance for cancer risk and treatment is reported in a recent review: *CYP1A1*, *CYP1A2*, *CYP1B1*, *CYP2E1*, *CYP2W1*, *CYP2A13* have been shown to have epigenetics component in their expression regulation (Rodriguez-Antona et al., 2010).

2.2 CYP2D6

CYP2D6 is the most extensively studied drug metabolizing enzyme in humans and its polymorphism was the first among polymorphic P450s to be characterized at the molecular

level. About 20-25% of clinically used drugs are metabolized by this enzyme including beta-blockers, antiarrhythmics, antidepressants, neuroleptics, analgesics and anti-cancer drugs. Most of them are metabolized to the inactive form; others like codeine, tramadol and tamoxifen are bio-activated. CYP2D6 is the only drug metabolizing CYP which is not inducible and therefore genetic variation plays a major role in the inter-individual variation in enzyme activity (Ingelman-Sundberg et al., 2007). The gene, located near two cytochrome P450 pseudogenes on chromosome 22q13.1, is highly polymorphic and more than 80 allelic variants related to the gene activity have been described (Zhou, 2009). The wild type allele is *CYP2D6*1* and major variants associated with decreased and abolished enzyme catalytic activity are *CYP2D6*2*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*10*, *CYP2D6*17* and *CYP2D6*41*. Multiple active gene copies are responsible for ultra-rapid metabolizer individuals. CYP2D6 phenotyping is characterized in vivo by the ratio of urinary amounts of parent compound relative to oxidative metabolite. The most commonly used probe substrates have been debrisoquine, sparteine and dextromethorphan. On the basis of the urinary metabolic ratio (MR), PM, UM, EM and IM phenotypes have been classified, but *CYP2D6* genotyping to predict metabolic status is considered a valid alternative to traditional phenotyping methods because genetic characteristics remain unchanged throughout life and are not influenced by environmental and physiologic factors (Gaedigk et al., 2003; Zanger et al., 2004). One of the most commonly used methods for *CYP2D6* genotyping consists in a combination of a first long-PCR (polymerase chain reaction) step designed to amplify the entire *CYP2D6* gene in a single fragment of about 5 kb followed by minisequencing, a multiplex PCR by SNP genotyping method (Fig. 1), screening the 11 most important polymorphic positions of the gene (Sistonen et al., 2005). The inferring phenotype from *CYP2D6* genotype information is based on different approaches including the conventional classification in PM, IM, EM and UM, established on the assumption of dominance, in which the phenotype is determined by the most efficient allele (Sistonen et al., 2007). However, this method does not consider inter-individual variability in urinary metabolic ratio-based phenotypes of subjects with identical genotype and the complexity of allele combinations. For this reason, the "activity score" (AS) system has been evaluated to translate genotype into a qualitative measure of phenotype and to overcome the difficulties of interpretation and comparison of different studies on CYP2D6 activity. For each variant allele a value is assigned based on CYP2D6 activity: "1" to the fully functional alleles and "0" to non-functional alleles, "0.5" or "0.75" to reduced activity alleles and double the value to duplicated genes. The AS is the sum of the individual allele values (Gaedigk et al., 2008).

2.2.1 Distribution of CYP2D6 polymorphism

Inter-ethnic differences in the distribution of *CYP2D6* genotypes have been described (Bernard et al., 2006; Gaedigk et al., 1999, 2002; Gaedigk & Coetsee, 2008; Griese et al., 2001; Kitada, 2003; Leathart et al., 1998; Luo et al., 2004; Wan et al., 2001; Zhou et al., 2009). In a worldwide survey (Sistonen et al., 2007) 5-10% of Europeans are PMs with the highest frequency of *CYP2D6*4* variant, while the UMs are most represented in North Africa and Oceania (40% and 26% respectively) due to the high percentage of gene duplication. In Asian populations alleles with absent CYP2D6 activity are very rare, but the **10* allele, causing a decreased enzyme function, occurs quite frequently leading to a high percentage of IMs. The **1* and **2* variants are the most represented in all population groups and their

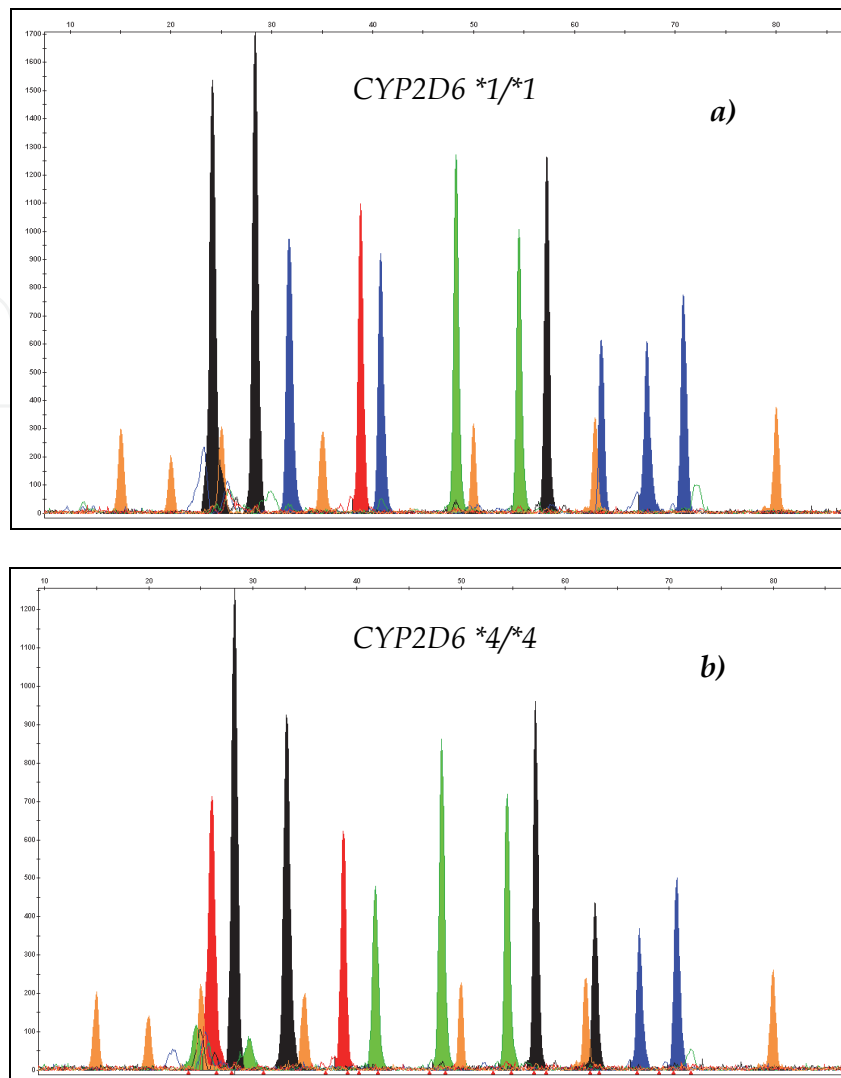


Fig. 1. Electropherograms of the multiplex PCR by SNP genotyping method (minisequencing) of two different individuals. Peaks correspond to 11 polymorphic positions (100C>T, 1023C>T, 1661G>C, 1707delT, 1846G>A, 2549delA, 2613-15delAGA, 2850C>T, 4180G>C, 2988G>A, 3183G>A) of the *CYP2D6* gene. *a)* Electropherogram of a homozygous *CYP2D6**1/*1 wild type genotype and *b)* Electropherogram of a homozygous *CYP2D6**4/*4 genotype

homogeneous geographic distribution could be regarded as the result of a long-term selective pressure maintaining the high frequency of alleles coding for a full-function enzyme. However, few rarely region-specific alleles associated with an altered enzymatic activity are observed and seem to be geographically dispersed over all four continents (Gaedigk et al., 2006, 2007, 2009, 2010; Luo et al., 2005). Ethnic specificity has become an integral part of pharmacogenetics research but caution is required against the use of continental labels to lump together heterogeneous populations. The Asian category, for example, is applied to individuals of distinct ethnicity and/or living in different countries or regions of the vast continent of Asia. Not surprisingly, significant variation in the distribution of pharmacogenetics polymorphism is detected among Asians (Suarez-Kurtz, 2008). Nevertheless, with increasing global migration, admixture gains relevance as an

additional challenge to the successful worldwide implementation of pharmacogenetics in clinical practice. The Brazilian population, with tri-hybrid ancestral roots in Amerindian, European and African groups and five centuries of extensive inter-ethnic mating, provides a valuable model for studying the impact of admixture on the conceptual development and clinical implementation of pharmacogenetics-informed prescription. Recognition of this fact is important in the design and interpretation of pharmacogenetics clinical trials in Brazilians, but does not imply that pharmacogenetics-informed drug prescription requires investigation of individual ancestry. Rather, individual genotyping should be directed to polymorphisms of proven clinical utility, irrespective of biogeographical ancestry (Suarez-Kurtz, 2010).

2.3 CYP2C9

CYP2C9 accounts for approximately 20% of total hepatic CYP content and metabolizes approximately 15% of clinically used drugs including S-warfarin, tolbutamide, phenytoin, losartan, diclofenac and celecoxib (Goldstein, 2001). To date, at least 33 variants of *CYP2C9* (*1B through to *34) have been identified (Yasar et al., 1999, 2002). *CYP2C9*2* and *CYP2C9*3* differ from the wild-type *CYP2C9*1* by a single point mutation: *CYP2C9*2* is characterised by a 430C>T exchange in exon 3 resulting in an Arg144Cys amino acid substitution, whereas *CYP2C9*3* shows an exchange of 1075A>C in exon 7 causing an Ile359Leu substitution in the catalytic site of the enzyme (Wang et al., 2009). The *CYP2C9* polymorphism is clinically highly significant and also substrate-dependent (Rosemary & Adithan, 2007; Xie et al., 2001). Marked inter-racial differences have been reported: *CYP2C9*2* and *CYP2C9*3* were both found with highest frequencies in Northern African and European populations. The frequency of *CYP2C9*2* decreases rapidly when moving from Europe toward the east, and it is practically zero in Eastern Asian populations. *CYP2C9*3* occurs more evenly in different geographic regions. (Sistonen, et al., 2009). The polymorphism in admixed populations was studied in the context of warfarin dose requirements. Variant alleles *CYP2C9*5*, *CYP2C9*6*, *CYP2C9*8* and *CYP2C9*11* occur in Africans but are rare or absent in Europeans. Genotyping of the six polymorphisms could be justified in Brazilians and, most likely African-Americans, but not Europeans, in whom only *CYP2C9*2*, *CYP2C9*3* might be adequate for predicting the *CYP2C9* polymorphism (Suarez-Kurtz, 2010). Candidate-gene association studies for warfarin response have identified *CYP2C9* and *VKORC1*, which codes for warfarin's target, vitamin K epoxide reductase, responsible for most of the genetic effect. *VKORC1* is a key enzyme of the vitamin K cycle and molecular target of coumarin anticoagulants. Among whites and Asians, *VKORC1* polymorphisms have shown a consistently significant influence on warfarin response, accounting for 11% to 32% of dose variability. Among North American blacks, *VKORC1* polymorphisms account for 4% to 10% of the variability in dose. Given that genetic diversity is known to be greater in persons of African descent, investigators have hypothesized that other *VKORC1* polymorphisms, or combinations of multiple polymorphisms (haplotypes), may better explain the variation in dose in this group (Limdi et al., 2010).

2.4 CYP2C19

The metabolism of tricyclic antidepressants, benzodiazepines and proton pump inhibitors is catalyzed mainly by *CYP2C19*. The most common genetic variation, designated *CYP2C19*2* (c.G681A), leads to a splicing defect that functionally affects the enzyme. Other alterations

have also been reported such as loss-of-function: *CYP2C19*3* (c.G636A; stop codon), *CYP2C19*4* (c.A1G; transition in the initiation codon), and *CYP2C19*5* (c.C1297T; amino acid substitution) (Santos et al., 2011). A variant defining an ultra-rapid metabolizer has been identified (Sim et al., 2006). Pronounced ethnic differences exist in the frequencies of the non-functional alleles: a low frequency of up to 5% in the Caucasian and African populations, higher in Oriental populations (23%). *CYP2C19*2* and *CYP2C19*3* are together responsible for the majority of PM alleles, of which *CYP2C19*3* is mainly found in Asians (Chen et al., 2008; Xie et al., 2001).

2.5 CYP1A2 and CYP2A6

CYP2A6 is an inducible enzyme primarily expressed in the liver and was first recognized for its involvement in the metabolism of coumarin. The *CYP2A6* gene locus spans a region of 6kbp and has been physically mapped to the long arm of chromosome 19. Thirteen allelic variants have been discovered due to point mutation, deletion, and gene conversion, and several of these result in altered enzyme activity. *CYP2A6* is involved in the metabolism of nicotine, some procarcinogens and several toxins. Variants may affect smoking, cancer and the treatment of cigarette smoking. (Xu et al., 2002). *CYP1A2* metabolizes clozapine, tacrine, tizanidine and theophylline, a number of procarcinogens like benzo[*a*]pyrene and aromatic amines, and several important endogenous compounds (e.g., steroids). *CYP1A2* is subject to reversible and/or irreversible inhibition by a number of drugs, natural substances and other compounds. The *CYP1A* gene cluster has been mapped on chromosome 15q24.1, with a close link between *CYP1A1* and *1A2* sharing a common 5'-flanking region. More than 15 variant alleles and a series of subvariants of the *CYP1A2* gene have been identified and some of them have been associated with altered drug clearance and response and disease susceptibility (Zhou et al., 2010).

2.6 CYP2B6 and CYP2C8

CYP2B6, mapped to the *CYP2* gene cluster on chromosome 19, plays a major role in the biotransformation of several therapeutically important drugs including cyclophosphamide, ifosfamide, tamoxifen, ketamine, artemisinin, nevirapine, efavirenz, bupropion, sibutramine and propofol. This enzyme also metabolizes arachidonic acid, lauric acid, 17 β -estradiol, estrone, ethinylestradiol and testosterone (Mo et al., 2009). Genetic polymorphisms in *CYP2B6* are defined in terms of 29 allelic variants many of which are associated with increased, decreased or abolished enzyme activity (Watanabe et al., 2010). Overall, there is a marked inter-individual variability in *CYP2B6* activity, but current pharmacogenetic knowledge is not sufficient to provide efficient tools to predict the specific capacity for metabolism of *CYP2B6* substrates (Ingelman-Sundberg et al., 2007). *CYP2C8* is a polymorphic phase I drug-metabolizing enzyme involved in the metabolism of several therapeutic drugs including paclitaxel, amodiaquine, troglitazone, amiodarone and verapamil, and has also been implicated in the activation of procarcinogenic compounds (Totah & Rettie, 2005). The gene is located on chromosome 10q24 in a cluster with *CYP2C19* and *CYP2C18* and 14 different allelic variants have been reported (<http://www.cypalleles.ki.se/cyp2c8.htm>). The main *CYP2C8* polymorphisms code for the amino acid changes I269F, R139K, K399R and I264M. These single nucleotide polymorphisms define three main non-wild-type alleles, *CYP2C8*2* (I269F), *CYP2C8*3* (R139K and K399R) and *CYP2C8*4* (I264M). The *CYP2C8*2* allele has been found in black populations with an allele frequency of 18% but is very rare in white subjects (Dorado et al., 2008).

2.7 CYP3A

The CYP3A drug-metabolizing enzymes facilitate the metabolism and elimination of a wide range of structurally different xenobiotics and of 50% of all clinically used therapeutic drugs. In addition, they participate in the metabolism of key endogenous substrates, such as retinoic acid, steroid hormones and bile acids (Domanski et al., 2001; Ingelman-Sundberg et al., 2007; Thummel & Wilkinson, 1998). The four CYP3A genes lie within a 218 kb region of chromosome 7q22.1 in the following order: CYP3A5, CYP3A7, CYP3A4, and CYP3A43 (Lamba et al., 2002; Westlind et al., 2001). More than 30 SNPs have been identified in the CYP3A4 gene (Du et al., 2006; Garsa et al., 2005). Generally speaking, variants in the coding regions of CYP3A4 occur at allele frequencies <5% and appear heterozygous with the wild-type allele. These coding variants may contribute, but are unlikely to be the major cause of inter-individual differences in CYP3A-dependent clearance, because of the low allele frequencies and limited alterations in enzyme expression or catalytic function (Eiselt et al., 2001). The most common variant, CYP3A4*1B, is an A-392G transition in the 5'-flanking region with an allele frequency ranging from 0% in Chinese and Japanese to 45% in African-Americans. Studies have not linked CYP3A4*1B with alterations in CYP3A substrate metabolism (Garcia-Martin et al., 2002; Lamba et al., 2002). CYP3A5 is polymorphically expressed in adults with readily detectable expression in about 10–20% in Caucasians, 33% in Japanese and 55% in African-Americans. The primary causal mutation for its polymorphic expression (CYP3A5*3) confers low CYP3A5 protein expression and its allele frequency varies from approximately 50% in African-Americans to 90% in Caucasians (Adler et al., 2009; Lamba et al., 2002). CYP3A7 is considered to be the major fetal liver CYP3A enzyme. Three of the mutations represent SNPs (CYP3A7*1B, *1D and *1E) and occurs in regions outside those associated with the regulation of CYP3A transcription. The fourth mutation (CYP3A7*1C) consists of the replacement of 60 bp from the CYP3A4 gene with the corresponding sequence from the CYP3A7 gene (Lamba et al., 2002).

3. Personalized therapy: ethical and legal issues

Current prescribing practice involves administration of a standard “one size fits all” starting dose and is often a process of trial and error, varying the prescription until the most suitable treatment is found (Sadee, 1998). However, such a procedure exposes the patient to possible side-effects. In fact, around 21% of all outpatients suffer some kind of adverse reaction to drugs prescribed by their physician (Queneau et al., 2007). By investigating drug metabolism related to individual genetic polymorphism, pharmacogenetics has a significant impact on the clinical setting so that forensic implications may arise throughout the public health sector. The concept of “therapy with the right drug at the right dose in the right patient” was highlighted just about ten years ago (Mancinelli et al., 2000) and pharmacogenetic tests are now available for a number of drugs by biotechnology companies, some with FDA approval, as reported in Wong et al., (2010): Luminex xTag® (Luminex Corporation, TK, USA), Roche AmpliChip® (Roche, Basel, Switzerland), Affymetrix DMET® chip (Affymetrix, CA, USA), Autogenomics INFINITI™ Analyzer (Autogenomics, CA, USA), Osmetech eSensors® (WA, USA), ParagonDx (NC, USA), and ABI PRISM® SNaPshot™ (Applied Biosystems, CA, USA) and TaqMan® assays (Applied Biosystems). In addition, the Authors underlined the limitations: existing evidence to demonstrate significant and medically relevant correlations for many disease-causing genes and variants, limited detection of genetic variants within the context of each testing

platform, clinical interpretation of genotype results including environmental factors, and transplanted organs interfering with testing. Nevertheless, SNP arrays covering 5 million SNPs will soon become a reality and the cost for whole-genome sequencing is rapidly decreasing (Sim & Ingelman-Sundberg, 2011). The influence of genetic polymorphism on drug failure or toxicity can be illustrated by some significant examples.

3.1 Moving to clinical practice: significant examples

An increasing number of studies on psychiatric patients have shown that genetic variation of *CYP2D6* and *CYP2C19* affects the metabolism of antidepressants and antipsychotics, thereby explaining the different therapeutic effects in different patients (Kirchheiner & Seeringer, 2007). Of the patients treated with antidepressants 10-20% react adversely and 25-35% do not respond to the medication. This can lead to treatment for patients being selected in what has been described as a "trial and error" fashion, as physicians try different pharmacological agents with their patients in order to select the best treatment (Morley & Hall, 2004). Given their selective mechanism of action, selective serotonin reuptake inhibitors (SSRIs) replaced tricyclic antidepressants and monoamine oxidase inhibitors, but because of their inhibitory effects on various CYP enzymes, SSRIs may be associated with clinically relevant pharmacokinetic interactions with other medications (Spina et al., 2008). In dementia, approximately 10-15% of direct costs are attributed to pharmacological treatment and only 10-20% of the patients are moderate responders to conventional anti-dementia drugs, with questionable cost-effectiveness (Cacabelos, 2008). Pharmacogenetic and pharmacogenomic factors are reported to be responsible for 75-85% of the therapeutic response in Alzheimer's disease (AD) patients treated with conventional drugs. Cholinesterase inhibitors of current use in AD, such as donepezil, tacrine and galantamine, are metabolized via CYP-related enzymes. EMs and IMs are the best responders, and PMs and UMs are the worst responders to pharmacologic treatments in AD. At this early stage of the development of pharmacogenomic/pharmacogenetic procedures in AD therapeutics, it seems very plausible that the pharmacogenetic response in Alzheimer's disease depends on the interaction of genes involved in drug metabolism and genes associated with Alzheimer's disease pathogenesis (Cacabelos, 2007). Paracetamol and tramadol were the most popular analgesics among individuals taking warfarin. A recent study supports clinical evidence of the significance of the adverse warfarin-paracetamol interaction, although the mechanism responsible for the interaction is not clear. Some case reports of warfarin tramadol interactions have been published and a *CYP2D6*-related mechanism has been proposed (Launiainen et al., 2010). Warfarin (4-hydroxy coumarin), the most frequently prescribed oral anticoagulant, has a narrow therapeutic index and a wide inter-individual variability in dose requirement: an increase or decrease in anticoagulant activity are associated with the risk of hemorrhagic or thrombotic events (Kamali & Wynne, 2010). Variants in the cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase (*VKOR*) genes have been shown to have a significant effect on warfarin dose requirement. Warfarin pharmacogenetics has become a case study for personalized medicine. Algorithms incorporating selected SNPs in two genes, *CYP2C9* and *VKORC1*, show improved dose prediction compared with algorithms based solely on clinical and demographic factors. However, the performance of these algorithms differs among racial groups, with a higher proportion of variability in dose explained in whites than in Asians or blacks. The first comprehensive assessment of the influence of six common *VKORC1* SNPs and haplotypes on warfarin dose among Asians, blacks and whites with the use of the largest racially

diverse cohort captured the influence of common genetic variation in *VKORC1* on variability in warfarin dose by a single polymorphism (either -1639G>A or 1173C>T) across all racial groups. Incorporation of additional *VKORC1* SNPs or haplotypes did not improve dose prediction. Therefore, current evidence supports the use of -1639G>A (or 1173C>T) to capture dose variability related to *VKORC1*. Both *VKORC1* and *CYP2C9* influenced warfarin dose among individual patients in all three racial groups studied (Limdi et al., 2010). The case of tamoxifen is well-documented in the management of women with hormone receptor (HR) positive breast cancer (Hoskins et al., 2009). Tamoxifen is a pro-drug that is metabolized to its main active metabolite endoxifen by the cytochrome P450 2D6. Null or reduced enzyme activity in women treated with tamoxifen results in worse outcomes in terms of cancer relapse and lower event-free survival rates compared to extensive metabolizers. Additional data are required for a mandatory use of a *CYP2D6* genetic test, considering the demonstrated potential effect of *CYP2C19* polymorphism on relapse risk during tamoxifen treatment (Sim & Ingelman-Sundberg, 2011). In addition, selective serotonin reuptake inhibitor antidepressant drugs such as paroxetine and fluoxetine have also been used to manage tamoxifen-induced hot flashes. These drugs potentially inhibit the metabolism of tamoxifen by *CYP2D6* and thus potentially may lessen the efficacy of tamoxifen (Singh et al., 2011). Recently, it has been pointed out that there is sufficient reason to be aware of the real possibility of herbal products inhibiting cytochrome P450 enzymes. Considering that self-administration of complementary products is an increasingly common trend worldwide, the interactions may significantly increase the risk of ADR (Sevior et al., 2010). The picture that emerges highlights the crucial role of the physician to understand when to order the pharmacogenetics test and how to use the results in clinical decision-making (Robertson et al., 2002). The authors emphasized that if the risk of side-effects from a drug is great, a physician who failed to order the test indicative of toxicity could be found to have been negligent and future lawsuits for failure to give a test or properly interpret it will ensue, both reflecting and reinforcing acceptance of pharmacogenetic testing as an ordinary part of medical practice.

3.2 Legal and ethical issues

The development of pharmacogenetics has important implications in the medico-legal and forensic field because the classic topics of informed consent, shared genetic information, privacy and data base collection arise (Vaszar et al., 2002). Nevertheless the problem of orphan patients, non-responders for all available drug options, might have unforeseen consequences to avoid the label "hard to treat" (Robertson, 2001). Some patients might not want to be tested for pharmacogenetics profiles and this leads to the question of what a physician should do if a patient refuses to be genotyped. The responsibility of health care professionals will need to be defined as to who (doctors, pharmacist, clinical chemists) is responsible for the application of new technologies (genotyping) and what kind of patient counseling is needed (van Delden et al., 2004). A recent paper (Hamburg & Collins, 2010) highlighted that today about 10% of labels for FDA-approved drugs contain pharmacogenomic information – a substantial increase since the 1990s. Furthermore, there has been an explosion in the number of validated markers but relatively little independent analysis of the validity of the tests used to identify them in biologic specimens. The National Institute of Health (NIH) and the FDA will invest in advancing translational and regulatory science, and will better define regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics, develop risk-based approaches for appropriate

review of diagnostics to assess their validity and clinical utility more accurately, and make information on tests readily available. As the field advances, they expect to see more efficient clinical trials based on a more thorough understanding of the genetic basis of disease. The impact on the medico-legal field is evident. But, there are two schools of thought on how tort liability may affect personalized medicine, i.e., whether fear of lawsuits will tend to accelerate progress or slow it down. Tort suits include product liability suits against manufacturers and negligence suits against physicians and other providers of health-related services (Evans, 2007). Recently, Wong et al. (2010) stressed that personalized medicine by means of pharmacogenomics may have a dramatic impact on the justice system in ways we are only beginning to understand. They stated that if personalized medicine has already entered the curricula of well-regarded medical schools such as that of Johns Hopkins University (MD, USA), law schools offer no analogue. For example, "The FDA relabelled some drugs such as warfarin with CYP2C9 and vitamin K epoxide reductase complex 1 to reduce bleeding. If pharmacogenetics retrospectively reveals that the warfarin patient was at high risk and testing was not initially performed, litigation may follow. Indeed, some lawyers advertise on the Internet for cases involving warfarin-related errors. Consequently, pharmacogenomics may become part of defensive medicine". An important issue for legal and ethical use of pharmacogenetic tests arises from the evidence of genetic polymorphism distribution in different ethnic groups. *CYP2D6* gene polymorphism shows that the distribution of PMs, IMs and UMs varies in different ethnic groups so inter-ethnic differences in drug response highlight the need to evaluate the genetic makeup of individuals before prescribing drugs, also considering that the recent demographic movements and back migration of populations are reshaping the picture of genetic diversity within the native population (Suarez-Kurtz, 2010). A recent review by McNamara (McNamara, 2008) discusses investigations of pharmacogenomics in heart failure and the challenge of converting genomic heterogeneity into a usable clinical tool, concluding that investigators are beginning to delineate the genomic basis for differences in drug efficacy between black and white heart failure cohorts. The influence of *CYP2C9* and *VKORC1* genotypes on warfarin dose requirements has been demonstrated in diverse racial and ethnic patient groups and to choose a warfarin starting dose, dosing algorithms have been developed that incorporate clinical, demographic and genetic information. Because of these significant issues, the Journal of Health & Life Sciences Law explored personalized or patient-tailored medicine addressing the relevance of genetic information, and how race and genetics have affected and may impact on the development of medicines, pharmacogenomics and personalized medicine in the United States (Braff et al., 2008). A second part discussed current and proposed federal and state laws and regulations intended to protect individuals from the misuse of genetic information, including uses that discriminate based on genetic predispositions (Braff et al., 2009). It was recently pointed out (Nebert et al., 2008) that numerous reasons exist to show that an "unequivocal genotype" or even an "unequivocal phenotype" is virtually impossible to achieve in current limited-size studies of human populations. The problem of insufficiently stringent criteria leads to a decrease in statistical power and consequently an equivocal interpretation of most genotype-phenotype association studies. It remains unclear whether personalized medicine or individualized drug therapy will ever be achievable by DNA testing alone. The authors ask "Where are we, today, in our understanding of the role of human genetics and genomics in drug toxicity, efficacy and therapeutic failure? Few high-prevalence predominantly monogenic genes that do make a difference in metabolism of various drug substrates (e.g.,

CYP2D6, *NAT2*, *TPMT*, *CYP2C19*) might contribute perhaps 15% to 20% to the (EM or PM) phenotype, whereas a contribution of 90% or more is expected for the gene responsible for a monogenic human disease. If we know that dozens or hundreds of additional downstream genes might affect the ultimate outcome of a particular drug, how can we integrate and assemble this knowledge into a diagram or equation?" A recent paper discussed the possible application of genotyping for depression, cardiovascular diseases and thromboembolic disorders, gastric ulcer, malignant diseases and tuberculosis (Tomalik-Scharte et al., 2008). The authors noted that thousands of manuscripts addressing pharmacogenetic questions in *in vitro* studies and clinical trials have been published, but it seems that the way to a broader use of pharmacogenetics approaches at the patients' bedside is quite laborious. The unknown exact relationship between the genotype and phenotype, although in many cases the genotype explains most of the inter-individual variability, the lack of prospective clinical studies in large patient cohorts and no reliable data on the cost effectiveness of screening procedures explain the slow progress in clinical pharmacogenetics/pharmacogenomics. In this respect, Zhou (Zhou, 2009) wrote that the functional impact of most *CYP2D6* alleles has not been systematically assessed for most clinically important drugs that are mainly metabolized by *CYP2D6*, though some initial evidence has been identified for a very limited number of drugs. The majority of reported *in vivo* pharmacogenetic data on *CYP2D6* are from single-dose and steady-state pharmacokinetic studies of a small number of drugs. Pharmacodynamic data on *CYP2D6* polymorphisms are scanty for most drug studies. Given that genotype testing for *CYP2D6* is not routinely performed in clinical practice and there is uncertainty regarding genotype-phenotype, gene-concentration and gene-dose relationships, further prospective studies on the clinical impact of *CYP2D6*-dependent metabolism of drugs are warranted in large cohorts. The expectation is that this research field will provide both the industry and clinicians with useful pharmacogenomic biomarkers that can aid in procedures for drug development and specific drug treatment in order to optimize the results and improve human health. The process is slow, and for a solid basis for decisions on mandatory biomarkers to be used further large prospective clinical studies are required. One fruitful manner in which this can be achieved is a closer collaboration between industry and academics (Johansson & Ingelman-Sundberg, 2011).

4. Forensic investigation

In the forensic context, pharmacogenetics can assist in the interpretation of drug-related deaths, especially accidental drug poisonings or cases of sudden death with "nearly normal autopsy" (Karch, 2007), called "white autopsy" in Italy. The author claims that the ability to identify "invisible diseases" with post-mortem genetic testing has become a reality far more quickly than anyone had ever imagined and this development is not without irony: "at the same time that many clinicians are expressing frustration about the lack of tangible gains provided by the Human Genome Project and pathologists are wondering about the viability of their field, DNA technology is about to reshape the field of forensic pathology". The role of pharmacogenetic analysis in forensic investigation has already been emphasized as the holistic approach of molecular analysis connected to macroscopic, microscopic and toxicological observations, constituting an integral part of modern medico-legal study of death (Koski et al., 2007). Nevertheless, the area of medico-legal investigation also involves occupational medicine due to the consequences on toxic-exposed workers. In this field the

role of *CYP2D6* genotype in determining parkinsonism resulting from pesticide exposure may play an important role (Elbaz et al., 2004). Pesticide exposure significantly increases the risk for Parkinson's disease even when the poor metabolizer allele is in the heterozygote state. Interestingly, poor metabolizers are less common in the Parkinson's disease group in rarely exposed subjects (Deng et al., 2004). Pharmacogenetics also plays an important role in drug-addiction studies: methadone is metabolized through the liver by cytochrome P450 enzymes *CYP3A4*, *CYP2D6* and *CYP1A2* and buprenorphine is mainly metabolized by *CYP3A4* enzyme. A recent review reported that Caucasians who lack *CYP2D6* function appear to be protected from oral opioid dependence since this genotype is under-represented in the opiate-addicted population and these poor metabolizers are satisfied with the withdrawal and anticraving relief provided by methadone treatment. Ultra-rapid metabolizer heroin-dependent patients have felt dissatisfied with methadone therapy and can do well using buprenorphine because it is not significantly metabolized by *CYP2D6* (Haile et al., 2008). In a limited number of cases of methadone toxicity, Wong et al. (2003) showed that the prevalence of poor metabolizers was higher but not significantly different from that of a control group (n=23). They concluded that *CYP2D6* mutations may not yet be directly associated with methadone toxicity, and pharmacogenomics, complementing other case findings in molecular autopsy, is considered an adjunct in interpreting the methadone toxicity of poor and intermediate metabolizers.

4.1 Post mortem analysis

Genetic variation and its effects on metabolism can be applied to post-mortem analysis to help resolve cases initially believed to be suicide or classified as sudden unexplained deaths especially in cases where poisoning, incapacitation, inebriation or certain diseases where pharmacotherapy is an essential treatment (such as epilepsy, depression, cardiac diseases or diabetes) are factors in the cause of death. An additional benefit is that pharmacogenetics analysis may provide health information (certainly only via proper ethical disclosure practices) to at-risk relatives (Budowle & van Daal, 2009). As reported recently, the medico-legal community has yet to fully exploit genetic variation as a parameter in determining the causes of death as done by the National Academy of Science in recognizing the underutilization of molecular autopsies (Sajantila et al., 2010). The authors of this valuable review stressed that an individual's pathophysiological phenotype affecting drug efficacy depends on genetic constitution and several other factors such as developmental stage, physiological and environmental factors, association with disease or specific conditions. Hence, some of these studies may be ethically unacceptable or practically impossible to perform in the clinical setting, but may be more readily performed post-mortem as part of the cause of death investigation or retrospectively with proper authorization. Therefore they recommend that serious consideration and support be given to studies of medico-legal genetics not just because of the impact on death investigation but because of the tremendous value such information can have for personalized medicine. From this point of view and due to the increasing attention paid to sudden cardiac death, the role of pharmacogenetics is now studied in more depth considering that cytochrome P450 enzymes in acquired Q-T prolongation are more prevalent than the congenital form. Several risk factors have been identified with use of Q-T prolonging drugs as the most frequent cause (van Noord et al., 2010). The *CYP2D6* hydroxylation capacity has already been implicated in causing elongation of the Q-T interval: patients treated with thioridazine that inhibits *CYP2D6* activity itself, may be prone to an increased risk of death due to sudden arrhythmia such as

“torsades de pointes” (Llerena et al., 2002). In general, fatal drug toxicity has been associated with either slow or ultra-rapid CYP2D6 metabolism depending on the substrate activation or inactivation. Sallee et al., (2000) described the clinical course of a nine-year-old boy diagnosed with attention-deficit hyperactivity disorder, obsessive-compulsive disorder and Tourette's disorder and treated with a combination of methylphenidate, clonidine and fluoxetine. After experiencing signs and symptoms suggestive of metabolic toxicity marked by bouts of gastrointestinal distress, low-grade fever, incoordination and disorientation for more than ten months, the patient presented generalized seizures, lapsed into status epilepticus followed by cardiac arrest and subsequently expired. At autopsy, blood, brain and other tissue concentrations of fluoxetine and norfluoxetine were several-fold higher than expected based on literature reports for overdose situations. The medical examiner's report indicated death caused by fluoxetine toxicity. As the child's adoptive parents controlled medication access, they were investigated by social welfare agencies. Further genetic testing of autopsy tissue revealed a gene defect at the cytochrome P450 *CYP2D6* locus, resulting in poor metabolism of fluoxetine. As a result of this and other evidence, the investigation of the adoptive parents was terminated. One of the first demonstrations that genetic variation in drug metabolizing enzyme can be analyzed in post-mortem blood was performed studying the *CYP2D6* gene variations correlated to the tramadol metabolite ratio in blood in 33 Finnish autopsy cases where tramadol was found (Levo et al., 2003). A series of fatal poisonings due to amitriptyline (AT) abuse not all due to suicides was reported in Finland in 2005 (Prahlow & Landrum, 2005). In view of this, Koski et al. (2006) investigated the genetic variation at *CYP2D6* and *CYP2C19* genes with the metabolic ratio of the drug in post-mortem samples. No cases of fatal poisoning due to a combination of AT treatment and poor metabolizer phenotypes was found, with the exception of one case of female suicide with a very high concentration of AT and homozygous null alleles at *CYP2D6*. The authors emphasized the role of confounding factors in the interpretation of pharmacogenetics results such as age and enzyme inhibition by drugs. The pharmacogenetics analysis in a post-mortem forensic setting to reveal the cause and manner of death demonstrated doxepin poisoning associated with a completely non functional *CYP2D6* genotype, considering that *CYP2D6* is a major factor involved in the large inter-individual variation in doxepin metabolism (Koski et al., 2007). However, ultrarapid metabolizer for duplication in *CYP2D6* may also be responsible for fatal toxicities. The risk of opioid poisoning to breast-fed neonates whose mothers had been prescribed codeine was studied after a fatal case. Neonatal morphine plasma concentrations were simulated for various combinations of *CYP2D6* genotype and morphine clearance. Neonates of mothers with the ultrarapid *CYP2D6* genotype and neonates of mothers who are extensive metabolizers have comparable risks of opioid poisoning (Willmann et al., 2009). A tragic case was reported in 2006 when a 13-day-old baby died from morphine poisoning. Review of the medical records revealed that the mother had been prescribed Tylenol® 3 (codeine 30 mg and acetaminophen 500 mg) in the immediate post-partum period. Initially she took two tablets twice daily, but she halved the dose on post-partum day two owing to somnolence and constipation. Following the development of poor neonatal feeding, the mother expressed milk and stored it in a freezer. Analysis of the milk for morphine using a specific enzyme-linked immunosorbent assay method for morphine revealed a concentration of 87 ng/mL. The mother was later classified as a UM of *CYP2D6* substrates, carrying one extra copy of a functional *CYP2D6* gene (Madadi et al., 2007). Since 2007, the FDA has required the manufacturers of prescription codeine products to include information on the label to inform prescribing doctors about these risks and to help prevent morphine overdose in

breast-fed infants. Recently, the death of a ten-month-old boy found dead in the bed after exposure to-ethylmorphine was reported. The morphine-to ethylmorphine ratio in blood from the deceased was higher than expected for the exclusive ingestion of ethylmorphine. The explanations considered that the metabolism of ethylmorphine involves both the de-ethylation to morphine by CYP2D6 and the conjugation to glucuronide by the glucuronosyltransferase UGT2B7. The activity of the enzymes varies for genetic reasons and is influenced by age. Infants have lower glucuronidation capabilities than adults and CYP2D6 activity may exceed adult levels in infancy. The CYP2D6 genotyping excluded the hypothesis of an ultra-rapid phenotype (Helland et al., 2010). Nevertheless, the genetic variability of CYP2D6 and possibly in UGT2B7 was studied in a large number of women receiving codeine for obstetric pain while breast-feeding. Breast-fed infants of mother who were CYP2D6 UM combined with UGT2B7 *2/*2 are at increased risk of potentially life-threatening central nervous system depression (Madadi et al., 2009). Molecular autopsy research was also performed on fentanyl that is clinically used as an adjunct to surgical anaesthesia or for chronic pain management and its toxicity may be partially due to CYP3A4*1B and 3A5*3 variant alleles, resulting in variable fentanyl metabolism. The study of 25 fentanyl-related deaths by the analysis of fentanyl and norfentanyl in post-mortem blood samples showed the first scientific evidence of CYP3A5 involvement in fentanyl metabolism: homozygous CYP3A5*3 causes impaired metabolism of fentanyl, and CYP3A4*1B and 3A5*3 variants may help to certify the fentanyl toxicity (Jin et al., 2005). Furthermore, pharmacogenetic analysis has gained burgeoning interest in suicidal cases both for the correlation with antidepressant therapy and in researching endogenous serotonin metabolism. A study of the genetic profile of individuals in relation to the presence of CYP2D6 and CYP2C19 genes in 242 fatal intoxications, 262 suicides and 212 natural deaths showed that those dying from suicide (including hanging, shooting, sticking/cutting or jumping from a height) included a higher number carrying more than two active CYP2D6 genes. A possible explanation was the lower concentration level of prescribed medication in these ultra-rapid metabolizers resulting in ineffective treatment, but no information was available on the medical history of the suicide cases (Zackrisson et al., 2010). Discussing the results of Isacson et al. (Isacson et al., 2009) and the treatment of depression with antidepressants, mainly SSRI, in preventing suicide, Bertilsson (2010) recently reported that the data seem to indicate that serotonergic mechanisms are involved in the etiology of suicidal behaviour. An alternative explanation to the overrepresentation of CYP2D6 gene duplication among suicide cases was based on the presence of the CYP2D6 enzyme in the human brain where its distribution follows that of dopamine nerve terminals, demonstrating several endogenous substrates of CYP2D6 among which of special interest is the O-demethylation of 5-methoxytryptamine to serotonin. The author reported that serotonin might then be synthesized in dopaminergic neurons by CYP2D6 and act as a false transmitter in wrong (inhibitory?) neurons.

5. Conclusion

Current pharmacogenetics research in the clinical and medico-legal settings provides new options for disease treatment and prevention of ADR avoiding correlated death, and for screening interactions with the polymorphic P450 enzymes early on in drug development. The ensuing information will be translated into routine clinical practice in the years to come benefitting millions of patients worldwide (Ingelman-Sundberg & Sim, 2010). In the future, the research in relatively new fields such as epigenetics and small nuclear RNA mediated

mechanisms will increase the number of useful biomarkers for personalized therapy. Indeed, epigenetics providing answers to interindividual variability in drug response not associated to genetic polymorphism, could represent the bridge that connects the environment to the genome (Gomez & Ingelman-Sundberg, 2009). In this respect, the area of pharmacoepigenomics has a promising future (Ingelman-Sundberg & Gomez, 2010). In medico-legal setting, molecular autopsy is becoming a reality also considering that robust techniques suitable for implementation in forensic laboratories are broadening the genetic analysis of P450 gene polymorphism. But we agree with Sajantila et al. (2010) that “in some ways this situation now confronting medico-legal geneticists is similar to the early years of the DNA level human identification era. The societal and judicial systems sought the technology and scientists had serious challenges to cope with demands. Like DNA-based identification at that time, fundamental pharmacogenetic research needs to be performed so that our knowledge is sufficient to render valid and reliable interpretations related to medico-legal genetic findings”. Significantly, Wong et al. (2010) state that personalized justice complements personalized medicine, but “personalized justice” in a firm foundation should be based on sound legal principles as well as reliable and valid evidence-based studies, not on ‘junk’ science and unsubstantiated case reports. Furthermore, the American Academy of Forensic Sciences supports the National Academy of Science’s 13 recommendations (National Academy of Sciences, 2009, as cited in Wong et al., 2010) and the following principles: the need for strong scientific foundations; laboratory accreditation; certification of technicians; the standardization of terminology; ethical protocols; governmental oversight; and the education of legal professionals, including judges, in forensic scientific methods and principles.

6. References

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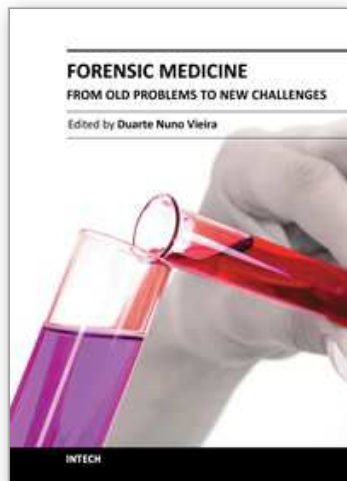
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Forensic Medicine - From Old Problems to New Challenges

Edited by Prof. Duarte Nuno Vieira

ISBN 978-953-307-262-3

Hard cover, 382 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

Forensic medicine is a continuously evolving science that is constantly being updated and improved, not only as a result of technological and scientific advances (which bring almost immediate repercussions) but also because of developments in the social and legal spheres. This book contains innovative perspectives and approaches to classic topics and problems in forensic medicine, offering reflections about the potential and limits of emerging areas in forensic expert research; it transmits the experience of some countries in the domain of cutting-edge expert intervention, and shows how research in other fields of knowledge may have very relevant implications for this practice.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Susi Pelotti and Carla Bini (2011). Forensic Pharmacogenetics, Forensic Medicine - From Old Problems to New Challenges, Prof. Duarte Nuno Vieira (Ed.), ISBN: 978-953-307-262-3, InTech, Available from: <http://www.intechopen.com/books/forensic-medicine-from-old-problems-to-new-challenges/forensic-pharmacogenetics>

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