We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

11

Pharmacogenetics Role in Forensic Sciences

Loredana Buscemi and Adriano Tagliabracci
Institute of Legal Medicine, Department of Neuroscience,Università Politecnica delle Marche, Ancona, Italy

1. Introduction

The completion of Human Genome Project and advancement of analytical technology with the large-scale identification of genome polymorphisms have contributed to the field of forensic science, especially in the studies on genetic basis of most important inherited arrhythmia syndromes responsible to sudden cardiac death, a major cause of death worldwide, and of individual differences in response to potential toxicants, with a new emerging area of interest, the so called pharmacogenetics.

The term pharmacogenetics was first used in the late 1950s (Clayman, 1952) and can be defined as the study of variability in drug responses as a function of genetic differences among individuals; applied to nontherapeutic foreign substances, collectively referred to as xenobiotics, the equivalent term toxicogenetics is used (Nebert, 1999; Mancinelli, 2000; Park and Pirmohamed, 2001; Roses, 2002; Wolf, 2000). The later coined term 'pharmacogenomics' usually refers to changes in gene expression as a consequence of drug exposure. However, the two terms, pharmacogenetics and pharmacogenomics, are often used synonymously.

One of the goals of pharmacocogenetics is the identification of the molecular genetic bases for interindividual variations in susceptibility to the anticipated effects of a drug or of xenobiotics (Pirmohamed and Park, 1999). If we want to provide a modern interpretation of the famous assertion of Paracelsus (1493-1541), it is true that "the dose makes the poison", but in different degrees, depending on the genetic characteristics of individuals.

There is no doubt that adverse drug reactions (ADRs) are a common cause of morbidity and mortality, despite extensive and well-regulated registration processes for proving drug efficacy and drug safety, and are associated with substantial costs of medical care (Lazarou, 1998; Pirmohamed, 1999).

Genetic studies could also clarify the origins of addictions, a diverse set of common, complex diseases, that are to some extent tied together by shared genetic and environmental etiological factors (Goldman, 2005; Kendler, 2003). The use and abuse of legal and illegal substances is a worldwide public health priority with repercussions extending from the level of the individual to the family, community, and society.

This chapter will focus on: a) adverse drug reactions; b) drug addiction; c) variability in the human genome; d) pharmacogenetic variability in drug response; e) genetic approaches to understand the individual differences in susceptibility to drugs/xenobiotics responses; f) ethical issues relating to the collection of genetic data.

2. Adverse drug reactions

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects; the risk of such effects ranges from near zero to high (Edwards, 2000). An adverse drug reaction (ADR), according to the World Health Organization definition, is "a response to a drug that is noxious, unintended, and undesired effect of a drug, which occurs at doses used in man for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function". This definition excludes therapeutic failures, intentional and accidental poisoning (ie, overdose), and drug abuse. Also, this does not include adverse events due to errors in drug administration or non-compliance (taking more or less of a drug than the prescribed amount); using this narrow definition avoids overestimating the ADR incidence (Lazarou, 1998). The terms adverse reaction and adverse effect are interchangeably, but must be kept in mind that is the "drug" that has an adverse effect whereas it is the "patient" that experience an adverse reaction. However, the two terms must be distinguished from "adverse event", that is an averse outcome that occurs while a patient is taking a drug, but is not necessarily attributable to it (Edwards, 2000).

The interest in ADRs was stimulated by the thalidomide tragedy in the 1960s and, over the past several years, ADRs have gained worldwide attention: the Food and Drug Administration (FDA) has planned a system of pharmacovigilance to be followed by regulatory agencies, pharmaceutical companies, and individual health care providers (U.S. Department of Health and Human Services Food and Drug Administration, 2005).

The occurrence of ADRs is associated with morbidity and mortality and substantial costs of medical care. Numerous studies provide a wide range of epidemiological data regarding adverse drug reactions. ADRs are one of the top ten causes of death in the United States, causing over 100 000 deaths annually; approximately 2–5% of all hospital admissions can be attributed to adverse drug reactions (Lazarou, 1998). In a study performed in 1999 in emergency departments of French public hospitals, out of a total of 1937 patients consulting, 328 (21%) of these patients consulted an physician because of an ADR (Queneau, 2007). During the year 2000, a prospective Italian study was performed in two observational periods of 10 days each in 22 Italian emergency departments: on 18 854 enrolled patients, 629 (3.3%) were affected by ADR and among these, 244 (38.8% of ADR patients) reported a serious event (Trifirò G, 2005). In a prospective Scandinavian study with 13.992 patients of internal medicine, the incidence of lethal ADR was estimated to be 0.95% (Ebbesen, 2001). Another prospective study conducted in the UK demostrated that about 6.5% of hospital admissions were ADR related in 18.820 patients (Pirmohamed, 2004). In a nationwide study in Spain, during a six-year period (2001-2006), the total number of hospitalized patients with ADR diagnosis was 350 835, 1.69% of all acute hospital admissions (Carrasco-Garrido, 2010); in The Netherlands, in 2001, 12 249 hospitalisations were coded as ADR related, 1.83% of all acute hospital admissions (van der Hooft, 2010).

Unfortunately, many physicians still consider adverse drug reactions to be an exception, rather than a primary diagnosis and adverse drug reactions have become cases of medical professional liability, with great increase of lawsuits (Wooten, 2010).

The classification of ADRs distinguished dose-related and non-dose related reactions, named type A and type B, respectively; type A reactions are common, predictable and therefore potentially preventable, based on the drug's pharmacological action, while type B reactions are more troublesome, uncommon and unpredctable. More recently, additional types were added, such as chronic (type C) and delayed (type D) effects, as well as

withdrawal or end of use syndromes (type E) and therapeutic failures (type F) (Edwards, 2000).

Different subjects with the same diagnosis could respond differently to the same drug administered at the same dose, with a diminished, absent or excessive response or interaction with other drugs (Mancinelli, 2000; Meyer, 2004). Potential risk factors for ADRs include patients' age, sex, race, nutritional status, organ function, especially of liver and kidneys, co-morbidities, co-medication, as well as some lifestyle variables (smoking habits, concomitant use of alcohols and drugs) and, of course, genetics. Some ADRs caused by genetic variation, previously considered unpredictable, may now be preventable. In general, genetic factors are estimated to account for 15-30% of interindividual differences in drug metabolism and response, but for certain drugs this can be as high as 95% (Evans, 2004; Weinshilboum, 2003)

ADRs may be reduced by means of the introduction of "personalized medicine", which anticipates the screening of patients for polymorphisms associated with a drug response, usually performed prior to the initiation of therapy. Despite significant progress in this field, only few drugs, such as cetuximab, dasatinib, maraviroc and trastuzumab, require a pharmacogenetic test before being prescribed: there are several gaps that limit the application of pharmacogenetics based upon the complex nature of the drug response itself (Gervasini, 2010).

This kind of policy foresees the introduction of new sophisticated tests, especially in the field of genetics, like DNA microarrays or DNA chips.

3. Drug addiction

Drug addiction is a chronic, relapsing disorder in which compulsive drug-seeking and drug-taking behavior persists despite serious negative consequences; continued use induces adaptive changes in the central nervous system that lead to tolerance, physical dependence, sensitization, craving, and relapse (Goodman, 2008). This mental health disorder imposes a significant burden on those directly affected, health care systems, and society in general, since it is associated with considerable morbidity and mortality, violence, and legal issues.

According to World Health Organization (WHO) figures, about 2 billion people worldwide consume alcoholic beverages, 1.3 billion nicotine and 185 million illegal drugs. In Europe the use of alcohol, nicotine and illicit substances is responsible for respectively 10%, 12% and 2% of the total cost of illness. (WHO, 2002).

Polydrug use of psychoactive substances, legal and illegal, characterizes and defines the style of consumption prevailing more and more common among younger subjects. There is another emerging market worldwide for an increasing number of psychoactive substances whose compositions are not well known and whose effects have not yet been recorded by physicians and they are difficult to recognize, delaying the diagnosis and treatment of patients themselves.

In addition there is another phenomenon in recent years: it is a marked shift in the marketing of licit and illicit drugs through online pharmacies, without requiring a prescription. The new generations are particularly vulnerable to this risk because they are very prone to use new technologies.

The nonmedical use of a prescription or over-the-counter (OTC) medication is another significant international emerging problem. OTC medications are pharmaceuticals that do not require a prescription and are sold on the shelves of markets, stores and pharmacies.

The several classes of medications that are commonly abused include: analgesics opioids, which are most often prescribed to treat severe pain (morphine, oxycodone, hydrocodone, hydromorphone, codeine); central nervous system depressants, commonly prescribed to treat anxiety and sleep disorders (barbiturates and benzodiazepines); stimulants, which are used primarily to treat attention defict disorder, attention defict hyperactivity disorder (ADHD) and narcolepsy (dextroamphetamine and methylphenidate). The OTC medicines, such as certain cough suppressant (dextromethorphan), sleep aids (doxylamine), antihistamines (diphenhydramine), decongestants and others can be abused for their psychoactive effects (Lessenger, 2008).

According to figures reported by NIDA, in 2009 approximately 7 million (M) reported past month non-medical use of psychotherapeutic drugs (2.8 percent of the U.S. population). The medications most commonly abused are: pain relievers (5.3 M), tranquilizers (2.0 M), stimulants (1.3 M), sedatives (0.4 M). The abuse of drugs is particularly problematic in adolescents, shows that in boys aged 12 to 17 years 8,3% reported abuse of Vicodin (hydrocodone) and 5% of Oxicontin (oxycodone hydrochloride) (NIDA, 2010).

All substances that are abused have ability to induce dependence and withdrawal.

The current challenge is to transfer the important increase of the knowledges of addiction's neurobiology in patients with addiction problems and to identify specific genes responsible for the particular vulnerability or resistance to addiction. Some schools of thought contend that addiction is entirely preventable through proper legislative action and individual choice, and claim that genetic research in this field is to assume a role as a low priority (Merikangas, 2003). Genetic research, however, plays a very important role, since the origins of addiction susceptibility are complex and wide-ranging; the underlying genetic factors need to be identified to solve the puzzle of what causes these pervasive and relatively intractable disorders (Goldman, 2005).

Both genetic and environmental variables contribute to the initiation of use of addictive agents and to the transition from use to addiction (Bevilacqua, 2009). Evidence from twin and adoption studies suggest that 40-60% of the risk of developing substance abuse disorders is due to genetic factors, with the percentage depending on the substance (Nestler, 2000). The addiction are complex disorders involving multiple genes and environment interaction (G x E). The genetic influences are more prominent in the later phases of individuals' progression toward substance dependence; this variation could add to allelic variations that could produce effects on addiction susceptability phenotypes by other routes that could include: differences in pharmacokinetic characteristics of the substance such as metabolism and biodistribution; differences in drug's rewarding properties; differences in traits manifest by the addict, including personality differences; differences in addict's psychiatric comorbidities (Uhl, 2004). This suggests two broad types of genetic predisposition to addiction: genetic profiles that make people more likely to find the acute effect of drugs rewarding and genetic profiles that make people more or less likely to developing addiction if they use drugs (EMCDDA, 2009). Finally, evidence indicates that there is a genetic predisposition that is shared between the different substance use disorders; nearly 25-36% of the genetic influences of alcohol, nicotine and cannabis problem use is attributable to overlapping factors (Young, 2006).

The inheritance of addictions has been evaluated in many ways, including studies on families and adoptees, but the main reference of our knowledge comes from the patterns of correlations in monozygotic (MZ) and dizygotic (DZ) twins. The overall genetic influence for substance use disorders has proved to be consistent and heritabilities for most substance

use disorders are estimated to be moderate to high (Wong, 2008). This moderate to high inheritance may seem paradoxical: addiction depends initially on individual choice to use an additive agent. Cocaine and opiates, among the most addictive of substances, are among the most heritable; in contrast, hallucinogens, are among the least addictive, and are also the least heritable (Bevilacqua, 2009).
The genes involved in the of the condition are very numerous (Kreek, 2005).
The phenotype for addiction to drugs is not well defined, and the heritability of addiction to drugs of abuse is far from clear. Knowledge of genetic factors in etiology and treatment response may enable the individualization of prevention and treatment, as well as the identification of new therapeutic targets (Buckland, 2008).

4. Variability in the human genome

Individuals are all different from each other and much of this difference has a genetic basis. Two unrelated human beings also share 99.9% of their genomic sequence, and could be considered genetically almost identical: the difference has been estimated to be of 0.1% overall, but still, this means that there are at least several million nucleotide differences per individual. There are, on average, three million genetic differences between any two people; the human genome contains approximately 3 billion base pairs of DNA and the variability of genetic material between any two individuals averages approximately one variation for every 1,000.
This genetic diversity in most cases have no functional significance, but in some cases have important consequences (Marchant, 2003). The most dramatic examples are seen with inherited disorders, where small alterations in gene sequence can result in premature death or severe disability (Alberts, 2002; Habener and Williams, 2002; King, 2002). It is also responsible of the phenotypic diversity, which results in the heterogeneous capacity of each individual to respond to exogenous substances, such as drugs and xenobiotics, and in the different susceptibility to induce adverse health effects.
The types of genetic variations used in these studies have changed in the past 25 years and can be classified into five major classes: RFLP (restriction fragment length polymorphism), VNTR (variable number of tandem repeat), STR (short tandem repeat), SNP (single-nucleotide polymorphism) and CNV (copy-number variation); furthermore, construction of the international SNP database and recent development of high-throughput SNP typing platforms enabled us to perform genome-wide association studies, which have identified genes or genetic variations susceptible to common diseases or those associated with drug responses (Nakamura, 2009).
SNPs are found at a frequency of about 1:1000 bases in humans and they are changes in a single base at a specific position in the genome, in most cases with two alleles. By definition, the more rare allele should be more abundant than 1% in the general population; if the variant is rare, with a frequency below 0.1%, it is referred to as a mutation. More than 99% of these genetic variations are biologically silent, while some polymorphisms can affect biological function according to their position within the genome.
Following the scheme of Orphanides and Kimber (2003), it is possible to distinguish:

1. SNPs that fall within the coding region of a gene can give rise to a protein that has an amino acid substitution, or is truncated, causing a change in activity, localization, or stability;

2. SNPs that induce shifts in translational reading frames will lead to the synthesis of proteins with altered aminoacid sequence and, perhaps, activity;
3. nucleotide alterations in the regulatory regions of a gene can also have a significant impact on the integrity of protein function;
4. polymorphisms in promoter regions may change the regulation and level of expression of a protein, whereas those that fall near intron-exon junctions may cause alterations in mRNA splicing;
5. more dramatic polymorphisms involving larger segments of the genome include gene deletions, gene conversions, and gene duplications (Orphanides and Kimber, 2003).

5. Pharmacogenetic variability in drug response

Gene polymorphisms account for the polymodal distribution of the frequency of response to a drug in a non-homogeneous population, i.e. one encompassing multiple genetic profiles capable of affecting response.

Current pharmacogenetic studies are exploring individual responses to drugs in relation to the genetic variations in the proteins involved in pharmacokinetics (absorption, distribution, metabolism and excretion) and pharmacodynamics (receptors, ion channels and other enzymes) (Roses A, 2000; Nebert, 2008) (figure 1).

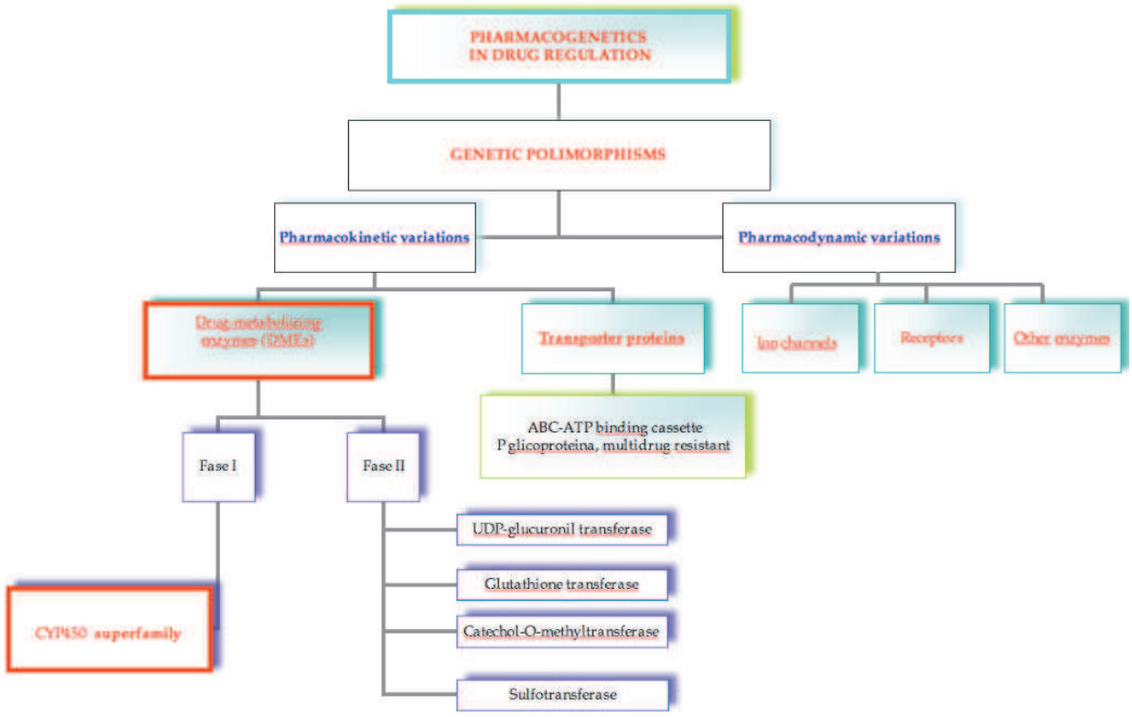


Fig. 1. Pharmacogenetic variations affecting the individual response to a drug

Drug-metabolizing enzymes (DMEs) play a key pharmacokinetic role (Meyer, 1997). Drugs are turned to metabolites in the liver, by transformation of functional groups (phase I reactions) and subsequent conjugation with endogenous lipophilic substances to form

inactive compounds (phase II reactions) for ready excretion in urine or bile. Oxidative drug metabolism is mainly catalyzed by the enzymes of the large CYP450 gene family, that contains 57 functional genes and 58 pseudogenes playing an important role in the metabolism of therapeutic drugs and other xenobiotics. CYP450 are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide. The corresponding genes are highly polymorphic and genetic variability underlies interindividual differences in drug response. CYP2D6, 2C19, and 2C9 polymorphisms account for the most frequent variations, since almost 80% of drugs in use today are metabolized by these enzymes (Danielson, 2002; Ingelman-Sundberg, 1999; Nebert, 2002; Nelson, 1999; Zhou, 2009). The polymorphisms of CYP2D6 significantly affect the pharmacokinetics of about 50% of the drugs in clinical use (De Gregori M, 2010).

The CYP450 enzimes convert the substances into electrophilic intermediates, which are then conjugated by phase II enzymes, of which the most important are the highly polymorphic UDP-glucuronil transferase, sulfotransferase, catechol-O-methyltransferase (COMT) and glutathione transferase, to facilitate substrate excretion by turning them into more water-soluble forms.

All these factors determine the trend of concentration over time and therefore the effectiveness of drugs and duration of effect. DME genetic variations result in marked phenotypic consequences; these range from poor metabolizers (where toxic drug effects may arise due to the absence of the gene product) to ultrarapid metabolizers (where therapeutic failure may be induced by the indicated dosage, with the risk of achieving high plasma concentrations and concentration-dependent side effects due to gene overexpression). The resulting phenotypes are poor (PMs), intermediate (IMs), extensive (EMs) and ultrarapid (UMs) metabolizers.

To leave the cell, some drugs are actively transported by membrane transporter proteins. The major transporter enzymes are MDR1 (multidrug resistance proteins), MRP (multidrug resistance-associated proteins) and OATP (organic anion-transporting polypeptides), where several genetic polymorphisms have been demonstrated. MDRs are transmembrane transporters of the large ABC protein family: P-glycoprotein (P-gp, or MDR1/ABCB1), the best known, is highly polymorphic. It can influence substrate absorption at the level of the blood brain barrier; high P-gp concentrations can limit entry of the required amount of drug, whereas low levels may result in abnormal accumulation. Recently, allele frequencies and findings regarding functional variants in drug transporter systems were reported in an interesting review (Kroetz, 2010).

Pharmacodynamic processes mediate the biochemical and physical effects of drugs on the organism. Variations in the sequence of the genes encoding the primary therapeutic target, such as receptors and ion channels, are capable of inducing protein forms with different functional characteristics. This can account for abnormal drug responses, which may also underpin some adverse reactions.

Recently, researchers are focusing on most important genetic variations that could contribute to the initiation of use of addictive agents and to the transition from use to addiction. The complex genetic constitution is partly accounted for by heterogeneity and polygenicity: the first assumes that a single or a few genetic variation(s) determine vulnerability and resiliency, but different alleles would lead to the same clinical presentation in different individuals; the second, on the other hand, assumes that a phenotype is a result of simultaneous function of multiple genetic variants (Goldman, 2005; Wong, 2008).

Pharmacogenetic studies can assess the effects of genetic variation on the risk for particular phenotypes for addiction, for example being an alcoholic (Onori, 2010; Buscemi, 2011). In recent years abundant evidence has accumulated demonstrating that alcoholism, a major health and social issue, being one of the most frequent disease and cause of premature death, is a multifaceted disease of the brain, caused by numerous genetic, neurobiological, environmental factors that are still not yet fully understood. Numerous genes are up- and/or down-regulated by alcohol exposure: the ethanol-responsive genes mainly encode functional proteins such as proteins involved in nucleic acid binding, transcription factors, selected regulatory molecules, and receptors. Currently there are only three medications approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of alcohol abuse and alcohol dependence: the aldehyde dehydrogenase inhibitor disulfiram, the micro-opioid receptor antagonist naltrexone, and the N-methyl-D-aspartate (NMDA) receptor inhibitor acamprosate (Wang, 2010).

6. Pharmacogenetic approaches

Pharmacogenetic studies can be categorized into two methodologic approaches: genome-wide linkage analysis and candidate gene approach.

Linkage analysis is applied to families with several affected individuals, to establish whether specific alleles of marker genes are found more often in individuals with the disease than in healthy subjects. The whole genome is analysed using markers that are uniformly distributed on all chromosomes, seeking chromosome regions that could contain genes involved in complex disorder susceptibility. The linkage is sought only in recent ancestors. Since only a small number of recombination events are involved, the gene regions detected by linkage analysis are likely to be large and to encompass hundreds or even thousands of genes. Genetic association studies assess correlations between genetic variants and trait differences on a population scale and they have been used widely to identify regions of the genome and candidate genes that contribute to complex disease.

A disease-associated SNP that falls within a gene can provide information on the mechanistic basis for disease, while a SNP that is in linkage disequilibrium with a genetic allele that confers disease predisposition may be used to identify susceptible individuals, and naturally this can include those genetic variations that influence relative susceptibility or resistance to toxicants (Roses, 2000). The common errors encountered in association studies of complex diseases are the small sample size, subgroup analysis and multiple testing, random error, poorly matched control group, failure to attempt study replication and to detect linkage disequilibrium with adjacent loci, overinterpreting results and positive publication bias, unwarranted candidate gene declaration after identifying association in arbitrary genetic region (Cardon, 2001). Despite these known limitations, the power of association analysis to detect genetic contributions to complex disease can be much greater than that of linkage studies (Risch, 2000).

Association studies can be distinguished into family-based, which use the transmission disequilibrium test, and population-based, which use case-control testing. Case-control studies compare genes from two groups of individuals, healthy and diseased. Ideally, the two groups should be homogeneous, with subjects matching for measures like age, ethnicity, years of education, and marital status, and differing only in terms of the disease studied. The allele frequency of the gene markers (e.g. SNPs) in or close to the genes are analysed and frequency differences between the groups taken to indicate that the gene contributes to the disease.

Association studies draw from historic recombination so disease-associated regions are extremely small in outbred random mating populations, encompassing only one gene or gene fragment. As the disease mutation is transmitted from one generation to the next, recombination will separate it from the alleles of its original haplotype.
A specific genetic profile, or haplotype, i.e. the combination of allelic states in a set of polymorphic markers found on the same chromosome, could be identified by association studies by analyzing a number of markers of a given chromosome region in a group of affected subjects and in a control group (case-control study). Different haplotypes can be found in a population as a result of mutation or genetic recombination. The recombination is principally determined by the genetic distance between markers and by the propierties of the locus where they are found (recombination hotspots). Markers that do not undergo recombination are characterized by linkage disequilibrium (LD). The tendency of some alleles at distinct loci to be co-inherited, due to reduced rates of, or absent, genetic recombination may lead to their association in a population, i.e. to LD. Recent LD studies by analysis of SNP haplotypes have suggested a block structure, at least in some portions of the genome. Haplotype blocks appear as regions made up of consecutive alleles that are co-inherited. Given the limited haplotype diversity within blocks, several SNPs will be redundant, enabling a minimum number of informative markers to be used to identify the common haplotypes in each block: these markers are called tag-SNPs. Different block structures can be found in different populations, with significant implications for association studies, since the tag-SNPs identified in a population will be useless in another if they are found in different blocks.

7. Ethical issues

It is necessary to make a reflection on how informations from the human genome will be used. The collection of genetic data has attracted much public attention for the possible ethical, moral and political issues relating to the use of these informations.
Genome-wide association studies trying to identify genes that contribute a small risk to common diseases can only be performed on an international scale; meanwhile, it is becoming more and more clear that genomic information is hard to hide. Thus the traditional promise in research that privacy will be protected appears to be less realistic. The deciphering of the genetic code may pose a threat to the protection of one's privacy; some variants that predict drug response are also markers for disease predisposition. This may subsequently lead to medico-legal implications, such as the issue of data confidentially: whether employers and insurance companies should given rights to assess the genetic data (Koo, 2006). Access to genetic might lead to discrimination of individuals with an unfavourable genetic constitution; for example, individuals who have a genetic predisposition for a certain condition, or who would only tolerate expensive drugs, might be charged higher insurance premiums (Vijverberg, 2010).
Most European countries have adopted genetic anti- discrimination legislation; Belgium was the first in 1990, and many countries followed. After a 13-year battle in Congress-longer than it took to map the human genome-the Genetic Information Nondiscrimination Act (GINA) was passed into law on 21 May 2008. Francis Collins, the director of the National Human Genome Research Institute, said that the success of personalized medicine hinged on the passing of the legislation.
Van Hoyweghen and Horstman state that many European genetic non-discrimination laws only provide the illusion of protection and the protection against potential risks of

discrimination based on predictive medical information is still so far. Some insurance companies may still use genetic test results or genetic information derived from physician records or insurance questionnaires (Van Hoyweghen, 2008). This practice is mainly caused by ignorance, confusion and misunderstanding, but also due to the lack of clear legal definitions of 'genetic data' and 'genetic tests'(Vijverberg, 2010). The definitions of genetic testing used by 65 organisations and entities, including genetics professional organisations, insurance organisations, pharmaceutical companies, and legal organisations, was reviewed; it was found that the definitions used were extremely variable; ranging from DNA testing solely, to any source that can provide unambiguous genetic information, including family history (Sequeiros, 2005).

It has been suggested that potential problems with the ethical use of this kind of genetic data can be minimized by selecting SNPs that are of pharmacogenetic and toxicogenetic value, while avoiding those that predict genetic disease (Roses, 2002).

Toxicogenetics can learn from the forensic sciences: the widely used technique of "genetic fingerprinting" uses a small number of highly polymorphic, unlinked genetic markers that have no known implications to the health of an individual (Orphanides and Kimber, 2003).

8. Conclusion

The potential of pharmacogenetics to improve the clinical practice is only at the very beginning but will present an important biomedical tool in the post-genomic era. The aim is to aid physicians in the prescription of the right medicine to a person in an attempt to obtain maximum efficacy and minum toxicity based on a genetic test, according the new strategy named "personalized medicine": prescribing the right drug in the right dose to the right patient according to specific health needs and individual characteristics.

Advanced diagnostic analyses, genetic counselling, and interdisciplinary and multidisciplinary approach, involving neurobiological, genetical, toxicological, psychological, and social sciences, should be integral parts of forensic practice.

Although a relatively novel concept in the forensic context, pharmacogenetics has the capability to assist in the interpretation of drug related deaths, particularly in unintentional drug poisonings where the cause of death remains unclear (Pilgrim, 2010). The recommendation number eleven of the report from the National Academy of Sciences (NAS) titled "Strengthening Forensic Science in the United States: A Path Forward" is concerned with improving medicolegal death investigations: "Best practices should include the utilization of new technologies such as laboratory testing for the molecular basis of diseases".

The forensic science community, however, has not yet fully received this directive and only few studies to date have been able to ascertain a correlation between genotype and phenotype for a limited number of drugs and to establish a link with the death (Koski, 2006; Koski, 2007; Launiainem, 2010; Levo, 2003).

The correlation between genotype and phenotype still remains a limitation in a molecular autopsy ant it is complicate for a number of reason. Only individuals completely lacking the enzyme activity (PMs) are highly correlated with the expected phenotype. There is substantial overlap in activity within and between the other phenotypic classes: subjects with identical genotypes may also exhibit different phenotypic activities which may be explained by population-specific factors, such as unidentified genetic, such as other enzyme and proteins, and non-genetic factors, such as diet. In addition, the funtional consequence of

the genetic variation may be substrate (e.g. drug or its metabolite) specific (Gaedigk, 2008; Sajantila, 2010).

The new opportunities, offered by pharmacogenetics, to analyse the genetic variations related to the risk of ADRs or to susceptibility to drug addiction are of considerable interest to forensic scientists, for their role in the evaluation of drug addiction in its various phases of development, from beginning to end stage. A better understanding of genetic susceptibility to addiction may be also useful for ascertaining the causes and circumstances of death. Some gene variants may, in fact, determine in some individuals more sensitive to the substance, with an increased risk of toxic effects, even death.

9. References

Alberts, B.; Johnson, A.; Lewis, J.; Raff, R.; Roberts, K. & Walker, P. (2002). *Molecular Biology of the Cell*, 4 th ed., Garland Publishing, ISBN 978-0815332183, New York

Bevilacqua, L. & Goldman, D. (2009). Genes and Addictions. *Clinical Pharmacology & Therapeutics,* Vol.4, No.85, (April 2009), pp. 359-361, ISSN 0009-9236

Buckland, P.R. (2008). Will we ever find the genes for addiction? *Addiction,* No.103, (April 2008), pp. 1768-1776, ISSN 0965-2140

Buscemi, L. & Turchi, C. (2011). An overview of the genetic susceptibility to alcoholism. *Medicine, Science & the Law*, in press, ISSN 0025-8024

Cardon, L.R. & Bell, J.I. (2001). Association study designs for complex diseases. *Nature Genetics*, Vol.2, No.2, (February 2001), pp. 91-99, ISSN 1061-4036

Carrasco-Garrido, P.; De Andrés, L.A.; Barrera, V.H.; De Miguel, G.A. & Jiménez-García, R. (2010). Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006). *BMC Health Services Research,* Vol.10, No.287, (October 2010), ISSN 1472-6963

Clayman, C.B.; Arnold, J.; Hockwald, R.S.; Yount, E.H.Jr.; Edgcomb, J.H. & Alving, A.S. (1952). Toxicity of primaquine in Caucasians. *The Journal of the American Medical Association,* Vol.17, No.149, (August 1952), pp. 1563-1568, ISSN 0098-7484

Danielson, P.B. (2002). The cytochrome p450 superfamily: biochemistry, evolution, and drug metabolism in humans. *Current Drug Metabolism*, Vol.6, No.3, (December 2002), pp. 561-597, ISSN 1389-2002

De Gregori, M.; Allegri, M.; De Gregori, S.; Garbin, G.; Tinelli, C.; Regazzi, M.; Govoni, S. & Ranzani, G.N. (2010). How and why to screen for CYP2D6 interindividual variability in patients under pharmacological treatments. *Current Drug Metabolism,* Vol.3, No.11, (March 2010), pp. 276-282, ISSN 1389-2002

Dressler, L.G. & Terry, S.F. (2009). How will GINA influence participation in pharmacogenomics research and clinical testing? *Clinical Pharmacology & Therapeutics,* Vol.5, No.86, (November 2009), pp. 472-475, ISSN 0009-9236

Ebbesen, J.; Buajordet, I.; Erikssen, J.; Brørs, O.; Hilberg, T.; Svaar, H. & Sandvik L. (2001). Drug-related deaths in a department of internal medicine. *Archives of Internal Medicine,* Vol.19, No.161, (October 2001), pp. 2317-2323, ISSN 0003-9926

Edwards, I.R. & Aronson, J.K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet,* Vol.9237, No.356, (October 2000), pp. 1255-1259, ISSN 0140-6736

Eichelbaum, M.; Ingelman-Sundberg, M. & Evans, W.E. (2006). Pharmacogenomics and individualized drug therapy. *Annual Review of Medicine,* No.57, (February 2006), pp.119-137, ISSN 0066-4219

EMCDDA Monographs (2009). Genetic susceptibility to addiction, In: Addiction neurobiology: ethical and social implications, A. Carter, B. Capps, W. Hall (Ed.), 47-50, Luxembourg, ISBN 978-92-9168-347-5. Available from http://www.emcdda.europa.eu/publications/monographs/neurobiology

Evans, W.E. & Relling, M.V. (2004). Moving towards individualized medicine with pharmacogenomics. *Nature*, Vol.6990, No.429, (May 2004), pp. 464-468, ISSN 0028-0836

Gaedigk, A.; Simon, S.D.; Pearce, R.E.; Bradford, L.D.; Kennedy, M.J. & Leeder, J.S. (2008). The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. *Clinical Pharmacology & Therapeutics,* Vol.2, No.83, (February 2008), pp. 234-42, ISSN 0009-9236

Gervasini G.; Benítez J. & Carrillo J.A. (2010). Pharmacogenetic testing and therapeutic drug monitoring are complementary tools for optimal individualization of drug therapy. *European Journal of Clinical Pharmacology,* Vol.8, No.66, (August 2010), pp. 755-774, ISSN 0031-6970

Goldman, D.; Gabor, O. & Ducci, F. (2005). The genetics of addiction: uncovering the genes. *Nature Reviews Genetics* Vol.7, No.6, (July 2005), pp. 521-532, ISSN 1471-0056 .

Goodman, A. (2008). Neurobiology of addiction. An integrative review. *Biochemical Pharmacology*, Vol.1, No.75, (January 2008), pp. 266-322, ISSN 0006-2952

Habener, J.F. & Williams, G. H. (2002). *Metabolic Basis of Common Inherited Diseases,* 1 st ed. W.B. Saunders, (Ed.), ISBN 978-072-1686-78-3

Ingelman-Sundberg, M.; Oscarson, M. & McLellan, R.A. (1999). Polymorphic human cytochrome P450 enzymes: An opportunity for individualized drug treatment. *Trends in Pharmacological Sciences*, Vol.8, No.20, (August 1999), pp. 342–349, ISSN 0165-6147

Kendler, K.S.; Jacobson, K.C.; Prescott, C.A. & Neale, M.C. (2003). Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *American Journal of Psychiatry,* Vol.4, No.160, (April 2003), pp. 687-695, ISSN 0002-953X

King, R.A.; Rotter, J.I. & Motulsky, A.G. (2002). *The Genetic Basis of Common Diseases*, 2 nd ed. (Oxford monographs on medical genetics, 44). Oxford University Press, ISBN 0-1951-2582-7, Oxford, UK

Koo, S.H. & Lee, E.J. (2006). Pharmacogenetics approach to therapeutics. *Clinical and Experimental Pharmacology and Physiology*, Vol.5-6, No.33, (May-June 2006), pp. 525-532, ISSN 0305-1870

Koski, A., Sistonen, J., Ojanperä, I., Gergov, M., Vuori, E., Sajantila, A (2006). CYP2D6 and CYP2C19 genotypes and amitriptyline metabolite ratios in a series of medicolegal autopsies. *Forensic Sciences International,* Vol.2-3, No.158, (May 2006), pp. 177-183, ISSN 0379-0738

Koski, A., Ojanperä, I., Sistonen, J., Vuori, E., Sajantila, A. (2007). A fatal doxepin poisoning associated with a defective CYP2D6 genotype. *The American Journal of Forensic Medicine and Pathology,* Vol.3, No.28, (September 2007), pp. 259-261, ISSN 0195-7910

Kreek, M.J.; Nielsen, D.A.; Butelman, E.R. & LaForge, K.S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscienze,* Vol.11, No.8, (November 2005), pp. 1450-1457, ISSN 1097-6256

Kroetz, D.L.; Yee, S.W. & Giacomini, K.M. (2010). The pharmacogenomics of membrane transporters project research as the interface of genomics and transporter pharmacology. *Clinical Pharmacology & Therapeutics,* Vol.1, No.87, (January 2010), pp. 109-116, ISSN 0009-9236

Lazarou, J.; Pomeranz, B.H. & Corey, P.N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *The Journal of the American Medical Association*, Vol.15, No.279, (April 1998), pp. 1200-1205, ISSN 0098-7484

Lessenger, J.E. & Feinberg, S.D. (2008). Abuse of Prescription and Over-The-Counter Medications. *Journal of American Board Family Medicine,* Vol.1, No.21, (January-February 2008), pp. 45-54, ISSN 1557-2625

Levo, A.; Koski, A.; Ojanperä, I.; Vuori, E. & Sajantila, A. (2003). Post-mortem SNP analysis of CYP2D6 gene reveals correlation between genotype and opioid drug (tramadol) metabolite ratios in blood. *Forensic Sciences International,* Vol.1, No.135, (July 2003), pp. 9-15, ISSN 0379-0738

Mancinelli, L.; Cronin, M. & Sadèe, W. (2000). Pharmacogenomics: the promise of personalized medicine. *AAPS PharmSci,* Vol.1, No.2, ISSN 1522-1059

Marchant, G.E. (2003). Genomics and Toxic Substances: Part II-Genetic Susceptibility to Enviromental Agents. *Environmental Law Review,* Vol.9, No.33, (September 2003), pp. 10641-10667

Meyer, U.A. & Zanger, U.M. (1997). Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annual Review of Pharmacology and Toxicology*, No.37, pp. 269-296, ISSN 0362-1642

Meyer, U.A. (2000). Pharmacogenetics and adverse drug reactions. *Lancet* Vol.9242, No.356, (November 2000), pp. 1667-1671, ISSN 0140-6736

Meyer, U.A. (2004). Pharmacogenetics-five decades of therapeutic lessons from genetic diversity. *Nature Review Genetics,* Vol.9, No.5, (September 2004), pp. 669-676, ISSN 1471-0056

Merikangas, K.R. & Risch, N. (2003). Genomic priorities and public health. *Science,* Vol.5645, No.302, (October 2003), pp. 599-601, ISSN 0036-8075

National Research Council (2009). *Strengthening Forensic Science in the United States: A Path Forward*. In: National Academies Press (Ed.), ISBN: 0-309-13131-6, Washington D.C.
Available from http://www.nap.edu/catalog/12589.html

Nakamura, Y. (2009). DNA variations in human and medical genetics: 25 years of my experience. *Journal of Human Genetics*, Vol.1, No.54, (January 2009), pp. 1-8, ISSN 1434-5161

Nebert, D.W. (1999). Pharmacogenetics and pharmacogenomics: Why is this relevant to the clinical geneticist? *Clinical Genetics,* Vol.4, No.56, (October 1999), pp. 247–258, ISSN 0009-9163

Nebert, D.W. & Russell, D.W. (2002). Clinical importance of the cytochromes P450. *Lancet,* Vol.9340, No.360, (October 2002), pp. 1155–1162, ISSN 0140-6736

Nebert, D.W.; Zhang, Ge. & Vesell, E.S (2008). From human genetics and genomics to pharmacogenetics and pharmacogenomics: past lessons, future directions. *Drug Metabolism Reviews*, Vol.2, No.40, pp. 187-224, ISSN 0360-2532

Nelson, D.R. (1999). Cytochrome P450 and the individuality of species. *Archives of Biochemistry and Biophysics,* Vol.1, No.369, (September 1999), pp. 1–10, ISSN 0003-9861

Nestler, E.J. (2000). Genes and addiction. *Nature Genetics, Vol.3, No* 26, (November 2000), pp. 277-281, ISSN 1061-4036

NIDA (2010). Prescription drug abuse. In: *Topics in brief*, Available from http://www.nida.nih.gov/tib/prescription.html

Onori, N.; Turchi, C.; Solito, G.; Gesuita, R.; Buscemi, L. & Tagliabracci, A. (2010). GABRA2 and alcohol use disorders: no evidence of an association in an Italian case-control study. *Alcoholism: Clinical and Experimental Research,* Vol.4, No.34, (April 2010), pp. 659-668, ISSN 0145-6008

Orphanides, G. & Kimber, I. (2003). Toxicogenenetics: applications and opportunites. *Toxicological Sciences,* Vol.1, No.75, (September 2003), pp. 1-6, ISSN 1096-6080

Park, B. K. & Pirmohamed, M. (2001). Toxicogenetics in drug development. *Toxicoogy Letters,* Vol.1-3, No.120, (March 2001), pp. 281–291, ISSN 0378-4274

Pilgrim, J.L.; Gerostamoulos, D. & Drummer, O.H. (2010). Review: Pharmacogenetic aspects of the effect of cytochrome P450 polymorphisms on serotonergic drug metabolism, response, interactions, and adverse effects. *Forensic Science, Medicine and Pathology, electronic only,* (November 2010), ISSN 1547-769X

Pirmohamed, M. & Park, B.K. (1999). The adverse effects of drugs. *Hospital Medicine,* Vol.5, No.60, (May 1999), pp. 348-352, ISSN 1462-3935

Pirmohamed, M.; James S.; Meakin S.; Green C.; Scott A.K.; Walley T.J.; Farrar K.; Park B.K. & Breckenridge A.M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *British Medical Journal.* Vol.7456, No.329, (July 2004), pp. 15–19, ISSN 0959-8138

Queneau, P.; Bannwarth, B.; Carpentier, F.; Guliana, J.M.; Bouget, J.; Trombert, B.; Leverve, X.; Lapostolle, F.; Borron, S.W.; Adnet, F. & Association Pédagogique Nationale pour l'Enseignement de la Thérapeutique (APNET) (2007). Emergency department visits caused by adverse drug events: results of a French survey. *Drug Safety,* Vol1, No.30, pp. 81-88, ISSN 0114-5916

Risch, N.J. (2000). Searching for genetic determinants in the new millennium. *Nature,* Vol.6788, No.405, (June 2000), pp. 847–856, ISSN 0028-0836

Roses, A.D. (2000). Pharmacogenetics and the practice of medicine. *Nature,* Vol.6788, No.405, (June 2000), pp. 857–865, ISSN 0028-0836

Roses, A.D. (2002). Genome-based pharmacogenetics and the pharmaceutical industry. *Nature Review Drug Discovery,* Vol.7, No.1, (July 2002), pp. 541–549, ISSN 1474-1776

Sajantila, A.; Palo, J.U.; Ojanperä, I.; Davis, C. & Budowle, B. (2010). Pharmacogenetics in medico-legal context. *Forensic Science International,* Vol.1-3, No.203, (December 2010), pp. 44-52, ISSN 1872-4973

Sequeiros, J. & Guimarães B. *Definitions of genetic testing, 3rd draft*. EuroGentest. 2005. Available from http://www.eurogentest.org/web/files/public/unit3/DefinitionsGeneticTesting-3rdDraf18Jan07.pdf (accessed February 2009).

Trifiro, G.; Calogero, G.; Ippolito, F.M.; Cosentino, M.; Giuliani, R.; Conforti, A.; Venegoni, M.; Mazzaglia, G. & Caputi, A.P. (2005). Adverse drug events in emergency department population: a prospective Italian study. *Pharmacoepidemiol and Drug Safety*, Vol.5, No.14, (May 2005), pp. 333-340, ISSN 1053-8569

Uhl, G.R. (2004). Molecular genetic underpinnings of human substance abuse vulnerability: likely contributions to understanding addiction as a mnemonic process. *Neuropharmacology,* No.47, Suppl.1, pp. 140-147. ISSN 0028-3908

U.S. Department of Health and Human Services Food and Drug Administration (March, 2005). Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. In: *Guidance for Industry*, 1.03.2010, Available from http://www.fda.gov/cber/guidelines.htm

Van der Hooft, C.S.; Sturkenboom M.C.; van Grootheest K.; Kingma H.J. & Stricker B.H. (2006). Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. *Drug Safety,* Vol.2, No.29, pp. 161-168, ISSN 0114-5916

Van Hoyweghen, I., Horstman, K. (2008). European practices of genetic information and insurance: lessons for the genetic information nondiscrimination act. *The journal of the American Medical Association*, Vol.3, No.300, (July 2008), pp. 326-327, ISSN 0098-7484

Vijverberg, S.J.H.; Pieters, T. & Cornel, M.C. (2010). Ethical and Social Issues in Pharmacogenomics Testing. *Current Pharmaceutical Design*, Vol.2, No.16, pp. 245-252, ISSN 1381-6128

Wang, L.L.; Yang, A.K.; He, S.M.; Liang, .J; Zhou, Z.W.; Li Y. & Zhou, S.F. (2010). Identification of molecular targets associated with ethanol toxicity and implications in drug development. *Current Pharmaceutical Design*, Vol.11, No.16, pp. 1313-55, ISSN 1381-6128

WHO (2002). The global burden. In: *Management of substance abuse,* Available from http://www.who.int/substance_abuse/facts/global_burden/en/index.html)

Wolf, C.R.; Smith, G. & Smith, R. L. (2000). Science, medicine, and the future: Pharmacogenetics. *British Medical Journal,* Vol.7240, No.320, (April 2000), pp. 987–990, ISSN 0959-8138

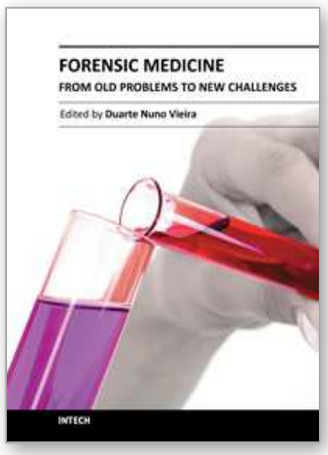
Wong, C.C.Y, Schumann. G. (2008). Genetics of addiction: strategies for addressing heterogeneity and polygenicity of substance use disorders. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences,* Vol.1507, No.363, (october 2008), pp. 3213-3222, ISSN 0962-8436

Wooten, J. M. (2010). Adverse Drug Reaction: Part I. *Southern Medical Journal,* Vol.10, No.103, (October 2010), pp. 1025-1028, ISSN 0038-4348

Young, S.E.; Rhee, S.H.; Stallings, M.C.; Corley, R.P. & Hewitt, J.K. (2006). Genetic and enviromental vulnerabilities underlying adolescent substance use and problem use: general or specific? *Behavior Genetics,* Vol.4, No.36, (July 2006), pp. 603-615, ISSN 0001-8244

Zhang, K.; Qin, Z.S.; Liu, J.S.; Chen T.; Waterman M.S. & Sun F. (2004). Haplotype block partitioning and Tag SNP selection using genotype data and their applications to association studies. *Genome Research,* Vol.5, No.14, (May 2004), pp. 908-916, ISSN 1088-9051

Zhou, S.F.; Liu, J.P. & Chowbay, B. (2009). Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metabolism Reviews,* Vol.2, No.41, pp. 89-295, ISSN 0360-2532



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:

Loredana Buscemi and Adriano Tagliabracci (2011). Pharmacogenetics Role in Forensic Sciences, 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/pharmacogenetics-role-in-forensic-sciences

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen