INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

PHARMACOGENOMICS -A MERE RENOVATION

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ABSTRACT

Pharmacogenomics is the study of the genetic basis for the differences between individuals in responses to drugs in order to tailor drug prescription to individual genotype. The present review article tells about the concept of pharmacogenomic nomenclature, polymorphism types, and systematic appropriate to understanding polymorphisms, Drug therapy for select therapeutic areas that highlight the applicability of pharmacogomics are presented including abacavir , selective serotonin reuptake inhibitors, tamoxifen, and warfarin. Challenges of translating pharmacogenomics into clinical practice included ethical, social, legal ,and economic issues. We have developed a pharmacogenomics education program to disseminate evidence-based pharmacogenomics informations and it tells about pharmacogenomics and its related concepts (biomarkers and personalized prescription). Next,the first generation of five DNA pharmacogenomic tests used in clinical practice of psychiatry are reviewed and about the curt type. initial attempts to use other microarray tests (measuring RNA expression) as peripheral biomarkent information on medicine-based evidence and cost-effectiveness usually focuses on average patients and not the outliers who are most likely to benefit from personalized prescription, and finally it also deals with SNP which helps in new drug discovery based on increasing knowledge of human genome.

Keywords: Pharmacogenetics; personalized prescription; cytochrome P450.

1. INTRODUCTION

Pharmacogenomics as broadly defined, is the study of the impact of genetic variation on the efficacy and toxicity of drugs, org prescriptions to individual genotype Pharmacogenomics is the study of the genetic basis for the differences between individuals in responses to drugs in order to tailor drug prescriptions to individual genotype. Optimum dose requirements for many drugs are known to vary among individuals. For example, the daily required dose varies 40-fold for propranolol and 20-fold for warfarin . Furthermore, drugs do not work in all patients; for example, 30% of schizophrenics do not respond to treatment by anti psychotics , and interferon B is only efficient in one out of three cases of multiple sclerosis . Adverse drug reactions also represent a major concern; in the United States alone, it is estimated that adverse effects are the fourth to sixth major cause of death and that hospitalizations due to adverse drug reactions cost from $US 30 billion to $US 150 billion a year . Moreover, adverse drug reactions are a major cause of non-compliance and failure of treatment, especially for chronic pathologies. Maximizing drug response while minimizing adverse effects for individuals through the study of gene variations is the goal of current pharmacogenomics. In the future, pharmacogenomics will be fully integrated into the drug development process in order to develop innovating and safe drugs. Here, we

review the scientific literature of 1998 and 1999 to look at the present and future value of pharmacogenomics.

1.1. HISTORY

The development of genomic medicine and genetic testing has helped in diagnosing some relatively rare and unusual disorders, but the field of pharmacogenomics is potentially much more important; it has been proposed as the driving force for implementing genetic medicine in primary care Vogel(1959) coined the term pharmacogenetics. According to Pirmohamed (2001), pharmacogenetics has been defined as the study of variability in drug response due to heredity and was largely used in relation to genes determining drug metabolism. More recently, the term pharmacogenomics is being used, which is a broader term encompassing all genes in the genome that may determine drug response. The distinction is arbitrary. Both terms are used interchangeably (Pirmohamed, 2001). Roses (2004) made an important distinction between two types of pharmacogenetics. Safety pharmacogenetics is aimed at avoiding adverse drug reactions (ADRs), which are usually called side effects in the psychiatric literature

2.PHARMACOGENOMIC STUDIES

These studies brought evidence that genetic factors were involve in variation are complex and the statistical outcome depends on a number of factors including the frequency of the trait (e.g. severe toxicity is often a rare event), the frequency of the allele within the populations studied, the number of contributing genes, the relative risk associated with the deleterious allele, and the density of markers used[1].The history of pharmacogenomic studies can be split in to three generations.

First generation studies examined a few candidate genes for which likely deleterious alleles and their biological consequences had been previously identified .Second generation studies, corresponding to present technology, still involve a candidate gene approach, but current technology has made it possible to simultaneously study more genes without any previous knowledge on their polymorphism.

The second and third generation studies are and will be based on high-density maps of markers, such as single nucleotide polymorphisms.

2.1Pharmacogenomics terms

Pharmacogenomics, This new science should eliminate the trial-and-error technique commonly used by physicians to find the right drug for an individual patient, and should limit the exposure of patients to drugs that cannot work for them. Pharmacogenomics will be used for patient selection and exclusion, and provide differentiation criteria. In short, pharmacogenomics is a science that is gaining recognition and respect and could be the most promising of the several disciplines that have arisen from genomics to deliver three main genomics-based products broadly defined, is the study of the impact of genetic variation on the efficacy and toxicity of drugs, or Specific examples are already emerging where the intervention of pharmacogenomics analysis is the study of how a patient's genetic makeup determines A prime example relates to the six major families of cytochrome P450 enzymes that are important metabolizing enzymes in the liver. These enzymes can be affected by exogenous substances; for example ,drugs can inhibit or induce the effectiveness of these enzymes. Just as importantly, drugs can be activated or inactivated by these enzymes. Thus, the variability of P450isozymes can lead to drug under exposure or over exposure the response to a therapeutic intervention. By contrast, no completely inactivating mutations have been found in the human CYP3A4isoform that is responsible for the majority of drug metabolism,although a common polymorphism in the promoter has recently been described[2,3].

2.2 Functional genomics

Functional genomics, the study of the relationships between particular genotypes and specific phenotypes, is an important discipline that defines the causative connection between a particular genotype and a specific phenotype However, recent studies suggest that the position and interaction of several SNPs in haplotypes might be more important to phenotype generation than single SNPs. Correlation of an individual's response to salbutamol was recently shown to be a result of multiple SNPs with in a haplotype and correlation with individual SNPs could not be established[3]

2.3 Pharmacoproteomics

mRNA Pharmaco proteomics is the study of patient sub typing on the basis of protein analysis. This mode of characterization is a more functional representation of patient-to-patient variation than is provided by genotyping, and includes the added effects of post-translational modification. Thus, pharmaco proteomics connects the genotype with the phenotype.This connection is not

always predictable on the basis of genotyping alone. Consider the effects of 'silent' SNPs, which refer to base-pair changes in RNA that do not produce an altered amino-acid sequence in the proteins that are encoded[4]. One way in which a silent SNP can alter the phenotype is by a change induced in folding.

2.4Pharmacotherapy

The anticipated and desired endpoint of pharmacogenomics is the ability to target a drug specifically to those patients who are genomically defined to respond well to the drug with no adverse effects.

3.NEW ADVANCES WITH PHARMACO GENOMICS

3.1SNP'S AND EFFECT OF GENETIC DIVERCITY ON DRUG ACTIONS

SNPs have several advantages over microsatellite repeat markers for fine mapping for four reasons. Firstly, SNPs are much more frequent than microsatellite repeats and occur, on average, once every 500–1000 bp, which means that there are about 3 million to 6 million SNPs spread through out the human genome[5]. Secondly, SNPs are less prone to germ line mutations, which means that their inheritance is more stable. Thirdly, SNPs can occur within coding or regulatory regions of genes, which means that they can be directly responsible for the traits studied. Finally, SNPs are mostly bi-allelic, which makes population frequency estimations easier development of large-scale SNP-based association studies is being hindered by the current lack of optimized genotyping and biostatistic tools. Large-scale association studies involving SNPs will only be economically feasible if high-throughput and affordable SNP scoring methods are developed[6]. It is clear that ,in order to achieve this, it will be necessary to develop methods that consume small quantities of reagents and DNA. High-throughput technologies are clearly headed towards increased miniaturization and integration of technologies such as robotics, Current SNP scoring is essentially based on PCR technology, analyzing either the variable nucleotide polymorphism (e.g. by single-nucleotide primer extension, restriction fragment length polymorphism-PCR, allele specific oligo nucleotide hybridization, or pyro-sequencing)

3.2Genetic variations and drug responses

Scientific literature contains an increasing number of examples demonstrating that gene sequence variations can cause modifications in drug efficacy and drug toxicity.

3.3Genetic variations and drug efficacy

Most drugs act by interacting with proteins such as receptors, enzymes, and intracellular signaling proteins. Over the years, it has been shown that these proteins present genetic variations that can affect sensitivity to drugs [7]

Asthma provides a good example of the use of pharmacogenomics in studying drug efficacy and toxicity.

3.4 Genetic variations and drug toxicity

Drug-metabolizing enzymes are known to influence drug toxicity. The main drug-metabolizing enzymes are cytochrome P450s (CYPs), for which genetic variations are known to influence drug toxicity and efficacy [7,8,9].

In addition to cytochrome P450, genetic variations of other phase I and phase II metabolizing enzymes contribute to variability in drug toxicity and efficacy[10,11].

During clinical trials, Zileuton (Zyflo) a 5-LO inhibitor that was being developed by Abbott Laboratories (Evry, France) was found to cause severe liver toxicity in 3% of patients treated. Genset, using SNP-based association studies.

4.MOLECULAR BIOLOGY AND POLY MORPHISAM

Briefly, a chromosome is the structural component of DNA that resides in the cell nucleus. Humans possess a total of 46 chromosomes (or 23 pairs). Each chromosome contains a single DNA molecule. DNA is the double-helix molecule, and segments or regions of DNA are known as genes. Genes contain non coding and coding nucleotide sequences needed for messenger ribonucleic acid (mRNA) transcription.

A nucleotide is a structural unit of DNA containing a sugar moiety, a phosphate group, and a base. Four nucleotide bases exist in DNA. The two pyrimidine bases are thymine (T) and cytosine (C), and the two purine bases are adenine (A) and guanine (G).16 Complementary base pair formation occurs when an A pairs with a T or when a G pairs with a C

4.1Polymorphism types

4.1.1Non synonymous SNP

A non synonymous SNP refers to when a nucleotide change occurs and the resultant amino acid has changed (Figure 1).Thiopurine methyltransferase (TPMT) is an enzyme that metabolizes thiopurine drugs (e.g., azathiopurine, 6mercaptopurine). The *TPMT*3A* polymorphism is an example of a non synonymous SNP for which the nucleotide guanine (G) is substituted for an adenine (A),

resulting in an amino acid change from alanine (Ala) to threonine

THE functional effect of the *TPMT*3A* polymorphism includes both non synonymous SNPs and results in decreased TPMT enzyme activity.

4.1.2Synonymous SNP

A synonymous SNP refers to when a nucleotide change occurs but the resultant amino acid is unchanged from the original or reference amino acid (Figure 1). A synonymous SNP is also known as a silent SNP. *ABCB1 3435 C>T* is an example of a synonymous SNP.2 Polymorphism of interest, functional effect, and population variation A patient's CYP enzyme activity may determine their ability to metabolize an SSRI. Patients who are poor metabolizers of CYP2D6 generally possess two copies of inactive *CYP2D6* alleles, which confers no CYP2D6 enzyme .*CYP2D6* alleles via a gene copy number variant polymorphism are considered ultra-rapid metabolizers and have the ability to metabolize drugs to a greater extent.

5. HUMAN GENOME AND BIO MARKERS

Human genome may have more than 20 000 genes and millions of variations, including the so-called single-nucleotide polymorphism(SNP). More recently, some authors have stressed that other types of genetic variations such as deletions or duplications, the so-called copy number variations (CNVs),may have been neglected (Redon et al,2006). More over, other less common genetic variations such as microsatellite polymorphisms and translocations, inversions, and substitutions may have relevance in pharmacogenomics

The Concept of Biomarkers: The FDA discussed the approval of pharmacogenomic tests as examples of biomarkers. Many definitions of biomarker exist, one of which is 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response(s) to a therapeutic intervention' (Wagner, 2002). There are different types of biomarkers, including pharmacogenomic biomarkers According to the FDA, the results of genetic tests that distinguish allelic variants of two metabolic enzymes, the CYP2D6 and thiopurine S-methyl transeferase (TPMT), were considered to be well established and, therefore, valid biomarkers (testing for both enzymes is described later in this article)

. Methodological/Scientific Issues in Diagnostic Testing

Some pharmacogenomics review articles (Grossman, 2007) insist on suggesting that the model developed by pharmaceutical companies, that of introducing a new drug into the market by sponsoring double-blind randomized trials, should be used as the ideal evidence-based model for introducing pharmacogenomic testing into the market.

This approach does not appear to be reasonable from the scientific point of view, as pharmacogenomic tests are not drugs which need to be proven effective in the controlled environment of a clinical trial with randomized and placebo design; they are diagnostic tests that must be proven useful in the complex clinical environment.

Despite these obstacles, the potential benefit of personalized prescription for some individuals is great. A recent large multicenter study using a randomized double-blind prospective design that was funded by a pharmaceutical company demonstrated that pharmacogenetic testing can be used to prevent a serious immunological ADR .

Although the design was simple, it eliminated the outliers, who were not included in the study. A major unresolved conceptual issue is that randomized clinical trials provide an average dose for an average patient whereas patients at the upper and lower ends of the response distribution (extreme outliers) tend to be ignored.

These are precisely the patients who most need personalized prescription and pharmacogenomic testing. If these subjects are quite rare, it is not easy to conduct prospective well controlled studies of them. Some subjects lack both CYP2D6 and CY After identification, they can be correctly treated using our current pharmacological knowledge (Johnson et al, 2006)

Large studies of these 'double' PMs are not likely to occur as they are o1 per 1000 in each race to identify 30 of them a sample of approximately 50 000 patients taking antidepressants would be needed (de Leon, 2007P2C19, which metabolize most antidepressants.

6. AMPLICHIP

The AmpliChip CYP 4 The microarray contains over 15 000 oligo nucleotide probes allowing testing for 20 CYP2D6 alleles, 7 CYP2D6 duplications, and 3 cytochrom CYP2D6 metabolizes several antipsychotic and antidepressant drugs (de Leon et al, 2006b; Kirchheiner et al, 2004). CYP2D6 is highly polymorphic, meaning that more than 60 alleles and more than 130 genetic variations (by combining SNPs and CNVs) have been

described for this gene, located on chromosome 22 (Ingelman-Sundberg et al, 2007, 2008). The activity level of the CYP2D6 enzyme, called the CYP2D6 phenotype, can vary widely due to different combinations of the various CYP2D6 alleles

The AmpliChip CYP 450 Test software uses algorithms to predict the four CYP2D6 phenotypes and two CYP2C19 phenotypes150 Test, which uses Affymetrix technology .

7. Pharmacogenomics in clinical practice

Pharmacists must consider multiple aspects when implementing pharmacogenomic evidence into practice. These aspects include but are not limited to access, feasibility, lack of sufficient evidence, and ethical, social, legal, and economic issues

Feasibility information such as the turnaround time for available pharmacogenomic test results or information about the sensitivity and specificity of these tests are not readily available. For example, approximately 5days are needed for *HLA-B*5701* test results to be available(G.M. Kuo, oral communications with Labcorp, January 15 to February 9, 2009). Up to 10 days are needed to determine *CYP2D6* and *CYP2C9* test results from the AmpliChip CYP450 test (G.M. Kuo, oral communications with Labcorp, January 15 to February 9, 2009)

Whole-blood specimen is recommended by most laboratories, although some accept buccal specimen (G.M. Kuo, oral communications with Labcorp, January 15 to February 9, 2009).

The lack of quality and number of long-term studies, small sample sizes of the clinical trial, and scant information about the predictive values of laboratory tests add to the challenges faced by health professionals in keeping up with practice information from the emerging pharmacogenomic.

7.1 Ethical issues

Selecting patients for pharmacogenomic tests must be evidence based to avoid genetic profiling, discrimination, stigmatization, or distributive injustice. Pharmacogenomic testing yields information that could help health professionals and patients make informed decisions about treatment options. cost effectiveness of pharmacogenomic tests exists Willingness to pay from the payers' perspective is varied, Economic issues Many unknown issues exist related to the economics of pharmacogenomic testing when translated into practice. For example, whether the patient or the insurance company should pay for the pharmacogenomic test

7.2 Pharm Gened program

Pharmacists need to obtain up-to-date pharmacogenomic information in order to interpret the literature and test results, make clinical recommendations and decisions, and provide counseling for patients. PharmGenEd is a 3-year program (2008–2011) designed to provide pharmacists, physicians, students, and other health professionals access to evidence-based pharmacogenomic information, increase their knowledge of pharmacogenomic testing for clinical application, influence their attitude to overcome barriers to discussing this topic with their patients, and improve their skills in using practice tools.

8. Challenges

The challenges to the industry created by pharmacogenetics and pharmacogenomics are significant and include the following:

• Genotyping will identify many new disease-related genes and provide an explosion of new targets to pursue; and

• Pharmacogenomics profiling will lead to patient stratification, and these new targets, as well as existing targets, will be divided into subsets.

It is estimated that genotyping will identify new disease related genes that will lead to between 5,000 and 10,000 new potential targets.

Because the current amount of targets is approximately 450 and is comprised of mainly four target classes, such as G-protein-coupled receptors (GPCRs), ion channels, nuclear hormone receptors and enzymes, these new targets will add genomic and medicinal diversity[12]

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9. CONCLUSIONS

9.1 Pharmacogenomics and the pharmaceutical industry

Furthermore, the Food and Drug Administration recently stated that 'companies aiming to market drugs with narrow therapeutic indexes may find delays in approval increasingly common if they fail to submit pharmacogenomic data pertaining to drug toxicity'.

It is up to companies in the pharmacogenomic business, clinical pharmacologists and regulatory agencies to convince pharmaceutical companies that pharmacogenomics can be a way to accelerate drug discovery and development, maximize the odds for drug registration as well as improve product positioning. The advantages of incorporating pharmacogenics in drug development are:

1. In preclinical development, pharmacogenomics can help pharmaceutical companies select better drug candidates by determining early on if a candidate is highly influenced by gene polymorphisms, thus reducing the risk of failure due to variable efficacy. It can also enable the development of diagnostics that will be used during clinical trials
2. In phase I clinical trials, genotyping individuals can help determine the influence of the polymorphisms on the pharmacokinetics of the drug a number of enzymes and transporters influence the processes of drug absorption and metabolism
3. In phase II clinical trials, genotyping individuals can help determine the influence of these polymorphisms on drug efficacy, and be used to stratify populations for phase III clinical trials, since a number of genes coding for proteins targeted by drugs (e.g. receptors, enzymes) have been shown to be polymorphic.
4. Once a protein has been found to cause variations in drug response, other proteins that interact with it or that are part of the same pathway can then be identified and potentially used as new drug targets[13].

It is reasonable to say that in the future, pharmcogenomics will allow not only individual prediction of drug efficacy and toxicity, but also the development of innovative, active and safe drugs.

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