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Pharmacogenetics: A Boon of Biotechnology

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ABSTRACT

Generally medicines or drugs are based on the concept "one medicine fits all". In other words medicines are given for a disease without looking into the constitution of the patient, except in some cases of allergy. However, it is now known that the response to a particular drug may differ in different patients suffering with the same disease. The study of how genetic differences of patients may influence the variability in the response to specific drugs is called as pharmacogenetics. It has been recognized that the presence or absence of response to a drug, and also its adverse side effects may sometimes to be attributed to reasons like mis- dosing, drug- drug interactions, allergy or medication error. However, it has been shown that efficacy and toxicity of many medications depend on genetic polymorphism in patients for drug metabolizing enzymes, transporters, receptors and other drug targets. These genes may also encode proteins involved in drug absorption, distribution, elimination and metabolism. Many of the genes determining the response to drug are non- disease and non- gene specific and are being studied in some detail. These studies have also shown that the drug response is polygenic in many cases, thus making their clinical study difficult. A study of these genetic polymorphisms is providing a strong scientific basis for optimizing drug therapy on the basis of each patient's constitution. Pharmacogenetics approach will allow all such cases to be dealt more appropriately, through a study of genetic basis of patients' response to medicines. In this review article I'll try to collect some important views and work of different workers on the pharmacogenetics and pharmacogenomics.

1. Introduction

The study of how genetic differences of patients may influence the variability in the response to specific drugs is described as pharamacogenetics. Actually it is the study of inherited genetic differences in drug metabolic pathway which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. The term pharmacogenetics is often used interchangeably with the term pharamacogenomics which also investigate the role of acquired and inherited genetics differences in relation to drug response and drug behavior through a systematic examination of genes, gene products, and inter- and intra- individual variation in gene expression and function. Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. The term pharmacogenomics first began appearing around the 1990s. The pharmacogenetic tests are performed to evaluate a person's potential response to a drug therapy. Most genetic tests have been developed to help diagnose or predict the development of a genetic disease, for forensic medicine purposes, and in establishing parentage.

Although early observations of unusual drug reactions based on biochemical individually were noted in the 1930s, the field of pharmacogenetics was not officially recognized until 1959 when the term "pharmacogenetics" was published by the German physician 'Friedrich Vogel'. Efficacy of major drugs used for several important diseases has been tested and the desired response of patients to these drugs varies from 25% to 80%. The significance and economic value of a simple predicted drug response, which will provide information on the likelihood of efficacy and safety of a drug for an individual patient, will change the practice and economics of medicine. This will make it necessary for a physician to prepare patients' profiles, and based on these profiles prescribe different discrete medicines concurrently for different patients with same disease. Further, the same disease phenotype may result due to different interactions of inherited metabolic variations. The science of pharmacogenetics is providing tools to classify the heterogeneity of disease. Thus, pharmacogenetics and/ or pharmacogenomics have already become an important area of biotechnology research to examine heterogeneity of disease and individual's responses to medicine.

2. Difference between pharmacogenetics and pharmacogenomics:

In general, **pharmacogenetics** usually refers to how variation in one single gene influences the response to a single drug. **Pharmacogenomics** is a broader term, which studies how all of the genes (the genome) can influence responses to drugs.

3. Pharmacogenetics and personalized medicine:

Personalized medicines also termed as precision medicine, is a medical procedure that separate patients into different groups- with medical decisions, practices,

interventions and/ or products being tailored to the individual patient based on their predicted response or risk of disease. While the tailoring of treatment to patients dates back at least to the times of Hippocrates, the term has risen in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding the molecular basis of disease, particularly genomics. However, personalized medicine and pharmacogenetics do not mean the same thing, because pharmacogenetics is only a part of these medicines, which include the risk of algorithms, molecular diagnosis, targeted therapies and, of course, pharmacogenetics.

The advantages of personalized medicines to patients are:

1. Higher probability of desired outcomes with a drug.
2. Low probability of untoward side effects.
3. Preventive strategies
4. Focused therapies
5. Reduced costs
6. Better health and better healthcare.

As personalized medicine is practiced more widely, a number of challenges arise. The current approaches to intellectual property rights, reimbursement policies, and patient privacy and confidentially as well as regulatory oversight will have to be redefined and restructured to accommodate the changes personalized medicine will bring to healthcare. Furthermore, the analysis of acquired diagnostic data is a recent challenge of personalized medicine and its adoption.

4. Pharmacogenetics in Medical practices:

The major task is identification of an optimized clinical candidate molecule among the many compounds synthesized by chemist after screening a drug discovery project. Such compounds are screened in a number of animal or cell models for efficacy and toxicity. The medical practice, a physician diagnoses the disease and prescribes a treatment on the basis of symptoms/ physical signs and appropriate tests (blood, urine, X- rays, NMR etc.). However, all patients suffering with a disease may not have same symptoms. Similarly same treatment may not suit all patients suffering with a particular disease. Therefore, pharmacogenetics and/ or pharmacogenomics intervention are needed in both cases.

According DeeAnn Visk PhD, as a practical matter, personalized medicine will be realized through intermediaries that can help clinicians work in accordance with the latest genomic knowledge. One such intermediary is the Clinical Pharmacogenetics Implementation Consortium (CPIC), an organization working to streamline the process of translating genetic test results into gene-based prescription recommendations.

Yogita A. Ghodke- Puranik and Jatinder K. Lamba show clinical implementation of pharmacogenomics in their book 'Innovative Approach in Drug Discovery". They observed that pharmacogenomics has the potential to influence clinically relevant outcomes in drug dosing, efficacy, and toxicity that can result in subsequent recommendations for testing. For many routinely used drugs, pharmacogenomics has provided inclusive evidence for such testing.

5. Drug Response of patients to medicines:

McCullam and Padmnabhan (2014) focused on the principles of pharmacodynamics and how genetic variations of drug targets can have an effect on drug response. According to them, generally, a patient may not exhibit all symptoms of a particular disease. Drug response refers to the pharmacodynamics (PD) response to the drug, which is all the effects of the drug on any physiologic and pathologic process, in relation to effectiveness and adverse reactions. Drug response or adverse effect is the net effect of multiple factors: age, organ function, concomitant therapy, drug interactions, and disease. In addition to these, there are now numerous examples of cases where inter-individual differences in drug response are due to sequence variants in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets. The study of the biochemical and physiological interactions between drugs and their targets and the relationship between plasma drug concentration and drug effect is known as pharmacodynamics. The genetic determinants of drug response are potentially of great clinical value as, unlike other factors influencing drug response, they generally remain stable throughout a person's lifetime.

Joshua C. Denny, Hua Xu (2014) observed genetic association with drug response. Drug-response phenotypes include adverse drug events and therapeutic efficacy. Serum drug levels can also be the phenotype of interest for genetic associations studies, especially when the drug level has direct therapeutic indications (e.g., warfarin for anticoagulation, antibiotics, or anti-rejection medications in transplant patients). Performing genetic association studies on drug response can be especially challenging. A key challenge is that the detection of a drug-response phenotype requires accurate identification of at least two "phenotypes"—the drug exposure and the outcome. In some cases, it requires resolving temporal sequences of more than two phenotypes. In addition, informatics tools such as MedEx, a medication information extraction system, have been applied to automatically extract drug dosing information for the warfarin pharmacogenetic study.

Susanne B. Haga, in Principles of Gender-Specific Medicine (Third Edition), 2017 have written about Drug response can be impacted by several factors including diet, comorbidities, age, weight, drug–drug interactions, and genetics. Individual genetic variation in key genes involved in the metabolism, transport, or drug target can contribute to risk of adverse events or treatment failure.

The study of genetic variation underlying pharmacokinetics and pharmacodynamics is known as pharmacogenetics, one of the pillars of the personalized medicine movement. However, the study of pharmacogenetics is not new; knowledge of the impact of genetic variation on treatment response has been known for decades. But with greater knowledge of key genes involved in drug metabolism and targeting and the ease of identifying genetic variation, the field has experienced a rebirth of sorts leading to new diagnostics to inform therapeutic decision-making. The US Food and Drug Administration (FDA) have developed a list of all drugs that include information about pharmacogenetics in the drug label, currently totaling more than 100 drugs.

Other factor that may impact drug response is the microbiome and epigenetic modifications. Drugs may impact the composition of the gut microbiome and the gut

microbiome can affect the expression of key liver enzymes involved in drug metabolism. Similarly, increasing research of the impact of epigenetics on health has also identified interaction between genetic variants and epigenetic modifications that can impact drug response. Thus, a more comprehensive predictor of treatment outcome may involve a joint analysis of epigenetic modifications and sequence variations.

6. Pharmacogenomics and pharmacogenetics:

Pharmacogenomics is the study that deals with the relationship between genomic variations and their effect on drugs. Though the terms pharmacogenomics (PGx) and pharmacogenetics (PGt) are often used interchangeably, pharmacogenetics usually refers to the effect of a single gene on drug response. Pharmacogenomics plays two major roles in precision medicine. First, it guides pharmaceutical companies in drug discovery and development. Second, it guides physicians in selecting the right drug for patients based on their genetic make-up, in avoiding ADR, and in maximizing drug efficacy by prescribing the right dose.

Genetic variations: The Human Genome Project (HGP), concluded in April 2003, revealed that humans have about 20,500 genes and that 99.5 percent of the genes are similar. The remaining 0.5 percent are variations that are responsible for the individual's eye color, blood group, predisposition toward particular diseases, etc. The most common type of DNA sequence variation found in the human genome is the single nucleotide polymorphism (SNP, pronounced "snip"). Another type of variation, called structural variations (SV), are deletions, insertions, tandem repeats, inversions, and copy number variations (CNV). There are approximately 11 million SNPs in the human genome, with an average of one every 1,300 base pairs. SNPs act as biological markers and determine an individual's response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing disease. Genetic differences among individuals can affect virtually all aspects of a disease and its treatment. Genetic variations can affect disease management with regard to the following: 1.The rate of disease occurrence, 2.The risk of disease progression or recurrence, 3.The drug or drug class most likely to provide benefit, 4.The therapeutic dose, 5.The nature and extent of beneficial responses to treatment, 6.The likelihood of drug toxicity.

Genetic variations relevant to drug development include:

- Genes relevant to the drug's pharmacokinetics (absorption, distribution, metabolism [including formation of active metabolites], and excretion)
- Genes that code for intended or unintended drug targets and other pathways related to the drug's pharmacologic effect
- Genes that can predispose to toxicities such as immune reactions
- Genes that influence disease susceptibility or progression.

All of these genetic factors can affect the benefit–risk drug profile.

7. The role of pharmacogenomics in precision medicine:

According to Rajasri Chandra (2017), personalized medicine, often called precision medicine, is a medical practice in which patients are prescribed medications that are appropriate to them, based on their genetic, environmental, and lifestyle factors. It is an approach, enabled by molecular diagnostics that contrasts with the traditional practice of treating all patients with the same disease with the same drug and with the same dosage. In fact, the practice is not really new. It was followed 2,500 years ago in ancient Greece by Hippocrates, the "Father of Western Medicine." As an interesting article by Sykiotis et al points out, Hippocrates believed in the individuality of disease and the necessity of giving "different [drugs] to different patients." He evaluated factors like a person's constitution, age, and physique, as well as the time of year, to decide how to, as it were, prescribe. Now we know that variations among individuals are due to differences in their genetic make-up. It is known that not all patients respond to the same drug in the same way. In the United States, adverse drug reaction (ADR) is the fourth leading cause of death, and it is estimated that prescription drugs are responsible for 2.74 million ADRs and 128,000 deaths annually. ADRs cost $136 billion yearly—more than the total costs of cardiovascular and diabetes care—and cause one out of five injuries or deaths per year to hospitalized patients.

8. Pharmacogenomics in drug development

To successfully develop personalized dosing regimens for patients, an understanding of pharmacokinetics (PK), pharmacodynamics (PD), and PGx is important. Every drug entering the body goes through the process of absorption, distribution, metabolism, and excretion (ADME). The sum of all these processes is PK, which determines how much of the drug is needed to reach the site of action for effective therapeutic outcome. The drug also causes physiological and biochemical changes in the body. PD is the mechanism of action of the drug and its effect on the body. It determines how well the target cells, such as heart tissue or neurons, respond to the drug. The drug manufacturer determines the intricate balance between the PK and PD so that the drug has the maximum intended effect and the minimal potential adverse effect on the patient. The innate genetic polymorphism in an individual can cause a shift in the balance of PK and PD, resulting in an alteration in the way the body and the drug (or its metabolites) interact with each other. PGx holds the promise that individuals can be given personalized medications guided by information on PGt testing, and the individual's environment, diet, age, lifestyle, and current state of health.

According to Allen D. Roses, "the role of physicians in making the necessary judgements about the medicines that they prescribe is often referred to as an art, reflecting the lack of objective data available to make decisions that are tailored to individual patients. Just over a hundred years later we are on the verge of being able to identify inherited differences between individuals which can predict each patient's response to a medicine. This ability will have far-reaching benefits in the discovery, development and delivery of medicines. Sir William Osler, if he were alive today, would be re-considering his view of medicine as an art not a science".

9. The future of medical practice in Pharmacogenetics

According to Klaus Lindpainther, there can be no doubt that the advances of molecular biology and molecular genetics and genomics, and of the associated methods and technologies, have had major impact on our understanding of biology and drug action, and that these tools are quintessential and indispensable for future progress in biomedicine and health care. The interface between these methods and concepts, and the discovery, development, and use of new medicines are being recognized as new 'disciplines', or facets of biomedical science, termed pharmacogenetics and pharmacogenomics.

Patrick N. Cunningham and Arlene B. Chapman published a paper on the future of pharmacogenetics in the treatment of hypertension Valuable genetic information is being discovered related to BP response to antihypertensive agents. However, translating these discoveries into clinical practice to improve treatment of HTN remains a challenge. While pharmacogenetics testing has made inroads in oncology, cancer is a situation where drug efficacy may have immediate impact on short-term survival and drug toxicity may be extremely severe. Primary care physicians treating the majority of HTN are likely to have considerable inertia and persist with the trial and error approach to BP management, given the multiple drug options available.

E. Mendrinou and G.P. Patrinos, consider the current drug development practices a relatively homogeneous group (i.e., all hypertensive subjects will respond similarly to the same medication) as the origin of patient populations, whereas specific studies are conducted when differences in drug response are anticipated, as in the case of organ (kidney and liver) impairment. Nevertheless, genetic variation may contribute an additional amount of variability to drug response. So while drugs in Europe and the United States are usually tested in Caucasian patients with defined disease states, medication doses are marketed for all patients, without distinction of their geographical origin and/or considering the heterogeneity of certain diseases. Thus the contribution of genetics to the variability in drug response is what the field of pharmacogenetics and pharmacogenomics aims to answer. The term "pharmacogenetics" was first coined by Vogel in 1959 to describe the inheritance of an aberrant drug metabolism. Pharmacogenetics has since been defined as the study of the variation in drug response as it relates to an individual's genetic makeup. Pharmacogenomics usually refers to a broader use of genome-wide association studies (GWAS) and potential complex interactions as well as alteration in gene expression that correlates to drug response. Both sciences deal with the germline heritable effects of the patient's genetic variation on drug response, and their goals are overlapping.

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