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Review Article

The foray of Pharmacogenomics-An India Perspective

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Abstract

Pharmacogenomics is the study of genetic differences responsible for the variability in response to drugs & metabolism among individual patients. The main interest or application of Pharmacogenomics is to permit the drugs to be tailor-made for every individual and adapted to each person's own genetic makeup, so that making a way for creating personalized drugs with greater efficacy and safety. This review aims to provide an overview of the value and scope of pharmacogenomics and personalized medicine in a developing country with severe health resource crunch and offers insights for the potential impact of this field on the safe and effective use of medications with its future prospects and challenges in a health set-up like India.

Keywords: Pharmacogenomics, India, Personalized medicine, human genome, clinical trials.

Introduction

In a large patient population, a medication that is proven efficacious in many patients often fails to work in some other patients. Furthermore, when it does work, it may cause serious side effects, even death, in a small number of patients. Although large individual variability in drug efficacy and safety has been known to exist since the beginning of human medicine, understanding the origin of individual variation in drug

response has proven difficult. The human genome sequence provides a special record of human evolution that varies among populations and individuals [1]. Sequence variations in drug target proteins, drug-metabolizing enzymes, and drug transporters can alter drug efficacy, drug side effects, or both to cause variable drug responses in individual patients [2]. The term Pharmacogenomics was introduced in 1995. It is a whole genome application, studying the total

variations in the human genome to the medications. The availability of the complete human genome sequence has made it possible to analyze the impact of variations of the human genome sequence on the pathogenesis of important diseases and the response to drug therapy at an accelerating rate in recent years. The rapid accumulation of knowledge on genome-disease and genome-drug interactions has also impelled the transformation of pharmacogenetics into a new entity of human genetics—pharmacogenomics—and, at the same time, provided a rationale for the hope that individualized medicine can be achieved in the near future [3].

Genetic variations that are common (occurring in at least 1% of the population) are known as polymorphisms, and mutations of a single nucleotide are known as single nucleotide polymorphisms (SNPs). More than one-third of human genes have been found to be polymorphic [4]. A change in the nucleotide sequence of a gene can lead to a change in the amino acid sequence of the protein that leads to altered enzymatic activity, protein stability, and binding affinities. Genetic variation thus affects drug efficacy of drugs when mutations occur in proteins that are drug targets (e.g., receptors), or are involved in drug transport mechanisms (e.g. ion channels) and safety when drug-metabolizing enzymes are involved [5].

Among the approximately 30,000 genes in the human genome, variations in the form of single nucleotide polymorphisms (SNPs) largely account for the variabilities among patients in their responses to drugs [6]. Arg16 and Gly16 polymorphisms in β 2-adrenergic receptor leading to responsiveness and non-responsiveness, respectively, to albuterol, a commonly used drug for Asthma, is a well known example of differential response to a drug. Ile359Leu polymorphism in CYP2C9 gene resulting in reduced drug clearance of warfarin (an anticoagulant used in patients with heart disease) and consequent death due to brain hemorrhage arising from overdose; CYP2D6 *4 polymorphism resulting in impaired metabolism of debrisoquin, a commonly used drug for hypertension, and a lethal lowering of BP; low activity allele(s) of thiopurine methyltransferase (TPMT) gene in lymphoblastic leukemia patients and transplant

recipients under treatment with azathiopurine leading to life threatening myelosuppression and hepatic toxicity are other common examples of varied drug response as well as adverse drug reactions [7].

Pharmacogenomics is thus the study of identification and analysis of genomic variations that affect the efficacy of a drug. Pharmacogenomic studies can potentially be predictive of an individual's drug-response or adverse reactions or susceptibility to iatrogenic disorders, and may also reveal new targets that can help in the design of new drugs.

Factors influencing Pharmacogenomics trials in India

Clinical trials need to be designed appropriately so as to identify not only individual but also population variations. Various factors impact a patient's response to a drug. These include not only his genotype, but also non-genetic and environmental factors, including sex, age, diet, lifestyle, and even the intestinal microflora [8]. Epigenetic changes can influence expression patterns in a time-, environment- and tissue-dependent manner. Circadian rhythms also markedly change gene expression patterns of many ADME genes (over 300 have been identified to date) thereby affecting pharmacokinetics and drug response in a time-dependent manner [9].

A study across 12 leading pharmaceutical companies from 1997 to 2011 demonstrated an average spending of \$5.8 billion per drug and trials account for nearly 60% of the drug development cost [10]. The Associated Chambers of Commerce and Industry in India (Assocham) has reported that almost 100 global and local pharmaceutical companies are conducting clinical trials in India, resulting in revenues of close to \$1.6 billion. With close to 150,000 people enrolled on the same, the norms for the conduct of these trials are going to become stricter in the near future. Diseases such as malaria, chicken guniya, tuberculosis, kala azar (visceral leishmaniasis) and head and neck cancer are more prevalent in India and trials need to be conducted to develop therapies to meet the needs of specific strata of populations [11]. An increasing number of these will be pharmacogenomic trials, involving biomarkers and companion diagnostics.

It is desirable to choose a genetically homogenous population as far as possible, as differences in ethnicity may impact the response to the drug. Appropriate population stratification is thus important. Irrespective of the type of trial, the biomarker should be evaluated for predictability and clinical validity [12].

The Department of Biotechnology (DBT) mandates that for a pharmacogenomic study to be conducted in India it should be of national relevance, and to meet this requirement, the disease under consideration should have a high prevalence in India. In addition, it is necessary that the drug under consideration should be a widely-used drug for the treatment of the disease, and the proportion of patients who either do not respond to the drug or do not elicit adverse reactions should be high [13].

Impact of Pharmacogenomics in India

India occupies 20% of the world population, but shares only 2% of the global pharmaceutical market and that too for generic drugs. This would mean that newer and probably safer drugs are out of reach of common Indians. Adverse drug reporting is also not a common practice in most of the clinical establishments in India [14].

An example of a selective response of sub-populations is that of “Ancestral North Indians” (ANI), which are genetically close to Middle Easterners, Central Asians, and Europeans, as compared to “Ancestral South Indians” (ASI), which are as distinct from ANI and East Asians, as they are from each other. It has been reported that up to 30 essential drugs are not effective on 13% of Northern India's population [15]. Thus, one could visualize that despite stratification of a huge and a genetically diverse Indian population, each segment would still represent a large enough slice to draw commercial benefits, and yet benefit society as well. The criticality would be to make this affordable to the masses and yet profitable to the industry, especially in a geography where there is very little healthcare coverage [16].

Various companies globally, including those in India, have started investing in pharmacogenomics [17]. Change management, patient and physician education, competitive pricing, regulations to ensure appropriate

informed consent processes, privacy protection concerning the use of genotype information in multiple studies and data ownership, are critical to support the growth of this domain to benefit India.

Benefits of pharmacogenomics

The era of genomics has opened new opportunities to discover new drug targets. This would ultimately lead to development of novel drugs and therapies that will be cost effective and safe for diseases/disorders. The current therapy which is evidence based would be replaced by “customized” therapy and thus will be very specific to treat major diseases like infectious diseases, cardio vascular disorders, diabetes, neurogenetic disorders, eye diseases, haemoglobinopathies etc [18]. The area also opened up potential commercial development of genomics research with pharmaceutical industries with the wealth of opportunities, the use of genetic analysis in the drug development process to understand the interaction between given drug a therapy and an individual genetic makeup; by using this information it is possible to design individual based drugs to reduce side effects and avoid adverse drug reaction[19]. Globally, several pharmaceutical industries are working in this area.

Improvements in the Drug Discovery and Approval Process - Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve [20].

Decrease in the Overall Cost of Health Care - Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets will promote a net decrease in the cost of health [21].

Availability of Better Vaccines - Vaccines made of genetic material, either DNA or RNA; promise all the benefits of existing vaccines without all the risks. They

will activate the immune system but will be unable to cause infections.

Improved Medicines - Pharmaceutical companies will be able to research for drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases [22]. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases.

Challenges of pharmacogenomics

India has recently established the Translational Health Science and Technology Institute (THSTI) at Gurgaon, Haryana as an emerging health biotech science consortium with the intent of translating science and technology into clinical practice [23].

There have been reports that the lack of exposure of molecular biology among doctors, the high costs of these tests as compared to the cost of treatment, longer turnaround times, the lack of bedside technologies, lack of skilled manpower and the smaller market size; and hence the lack of investment in marketing these tests, as some of the key challenges impacting the growth of pharmacogenomics in India.

Future prospects

Can insights into the genetic regulation of drug response lead to the identification of new therapeutic targets or to the more precise manipulation of known targets? Can the knowledge as to how genetics controls human drug variability be used to direct therapy to specific conditions in which a better response is probable? Can understanding genetic regulation of response and disposition of drugs in patients be used to improve drug safety by better understanding how adverse drug reactions develop, how these reactions can be modified or prevented and which patients are at specific risk for adverse drug reactions? While all three approaches should and are being pursued, it is likely that the most immediately fruitful results will come from applying pharmacogenomics to enhancing drug safety.

It is time to debate on how a developing country like India can channel its limited financial resources, knowing that the drug discovery programs and the drug response monitoring programs can be of huge

economic liabilities. The challenges are further aggravated by the genetic diversity of the resources for both, the natural product drug discovery programs and drug response monitoring programs. Knowing that the drug discovery programs are full of uncertainties, in contrast, the drug response monitoring is always a result-oriented initiative. Interestingly, India's pharmaceutical market, mostly deals with generic drugs, therefore, it further strengthens the view that drug response monitoring program based on pharmacogenomic profiling of Indian populations is ideal for having a safer response to medications. For pharmaceutical companies worldwide [24], India is not only a potentially huge market for drug therapeutics but is also a repository of important human genetic diversity. Understanding this diversity is valuable because it better defines those population subgroups that will benefit more from a particular drug than others.

Conclusion

Pharmacogenomics has a greatest history of achievements in various fields through treating simple and complex diseases and excellent works in cancer therapy. It accounts in diagnosing genetic information thus helping to predict not only patients drug response but also many other affects like adverse drug effects and their interactions and thus diseases related to that genes. In the future, pharmacogenetic researchers have the potential to subdivide each disease according to genetics, not symptoms. Specific diagnoses may be based on the molecular mechanisms involved rather than clinical presentation. Molecular mechanism differences will subdivide patient groups with common diseases like hypertension, diabetes, and cancer. Pharmacogenomics is already making an impact in a wide array of disease states and drug therapy; it will eventually become part of standard patient management in selecting and monitoring drug therapy. Pharmacogenomics will definitely help us to sharpen our medical and pharmaceuticals tools. Drugs will become more precise and efficient. Large collaborative efforts across biostatisticians, epidemiologists, pharmacologists and clinicians are needed to provide robust evidence to support individualized treatment for improved drug efficacy and safety.

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