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Review Article

PHARMACOGENOMICS: GENETIC APPROACH OF TAILORING PERSONALIZED MEDICINE

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ABSTRACT

Pharmacogenomics examines the genetic variation of patients which are seeking to drug administration. It is the branch which correlating the gene expression with a drug's efficacy or toxicity. It provides a more rational way for drugs to be discovered, developed, and delivered. Pharmacogenomics make assures that drugs might one day tailor–made for individuals and adapted to each person's own genetic makeup. Individual's genetic makeup is thought to be the key to creating personalized with greater efficacy and safety. A personalized medicine is a medical approach for a patient for the diagnosis of the cause of the disease based on the genetic profile of the patient with fewer adverse effects. The ultimate aim of personalized medicine is to individualize health care by using knowledge of patient's – health history, behaviours, environments and genetic variation. Pharmacogenomics helps to improve the diagnosis of the underlying cause of the disease and allow the selection of a specific drug treatment, with fewer side effects. In this review we will discuss about polymorphism based on genetic profile of the people to its molecular level and its future prospects.

Keywords: pharmacogenomics, genetic makeup, personalized medicine, single-nucleotide polymorphisms

INTRODUCTION

Pharmacogenomics deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity [1]. In a broader concept that combines the recent advances in DNA sequencing, genotyping and expression profiling with pharmacogenetics to provide a more rational way for drugs to be discovered, developed, and delivered [2]. Pharmacogenomics has been characterized as "getting the right dose of the right drug to the right patient at the right time"[3]. Pharmacogenomics can lead to the discovery of better drugs targeted at specific population sub-groups, as well as drugs that will work on all sub-groups. This involves understanding the mechanism-of-action of drugs on cells as revealed by gene expression patterns. Pharmacoproteomics is a more functional representation of patient-to-patient variation than that provided by genotyping [4]. With pharmacogenomics, the typical 'trial-and error' practice of dispensing medicine by physicians will be replaced with a standard procedure that includes genetic testing followed by a prescription tailored to each individual.

Pre-prescription genetic tests can be run to determine an individual's tolerance and ability to respond positively to a certain drug. Genetic tests will be effective in reducing ADRs especially in new treatments and in existing treatments with narrow therapeutic indexes.[5] Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety. The goal of personalized medicine is to individualize health care by using knowledge of patients' health history, behaviors, environments, and most importantly, genetic variation when making clinical decisions [6]. A personalized medical approach of a patient with disease will mean that the genetic profile of the patient will improve the diagnosis of the underlying cause of the disease and allow the selection of a specific drug treatment, which yields fewer serious adverse drug reactions [7]. Pharmacogenomics has the potential to dramatically reduce the estimated 100,000 deaths and 2 million hospitalizations that occur each year in the United States as the result of adverse drug response. [8]

Genetic polymorphism

Polymorphism in biology occurs when two or more clearly different phenotypes exist in the same population of a species, it is related to biodiversity, genetic variation and adaptation; it usually functions to retain variety of form in a population living in a varied environment. The term is also used somewhat differently by molecular biologists to describe certain point mutations in the genotype, such as SNPs (single nucleotide polymorphism substitutions). Genetic polymorphism is the simultaneous occurrence in the same locality of two or more discontinuous forms in such proportions that the rarest of them cannot be maintained just by recurrent mutation or immigration. Genetic polymorphism relates to a balance or equilibrium between morphs.

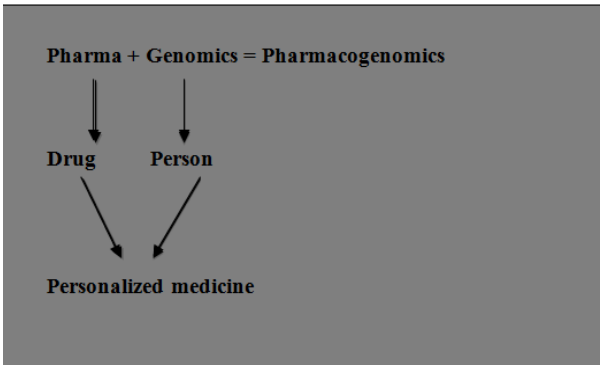

Fig.1: Diagrammatic view of Pharmacogenomics.

Molecular mechanisms of genetic polymorphisms

The most common genetic variants are single nucleotide polymorphism substitutions (SNPs). Single base pair substitutions that are present at frequencies of 1% or greater in a population are termed single nucleotide polymorphisms (SNPs) and are present in the human genome at approximately 1 SNP every few hundred to a thousand base pairs, depending on the gene region [9]. Coding nonsynonymous SNPs result in a nucleotide substitution that changes the amino acid codon, this could change protein structure, stability, substrate affinities, or introduce a stop codon. Coding synonymous SNPs do not change the amino acid codon, but may have functional consequences (transcript stability, splicing). Noncoding SNPs may be in promoters, introns, or other regulatory regions that may affect transcription factor binding, enhancers, transcript stability, or splicing. The second major type of polymorphism is indels (insertion/deletions). SNP indels can have any of the same effects as SNP substitutions: short repeats in the promoter (which can affect transcript amount), or larger insertions/ deletions that add or subtract amino acids [10]. Indels can also involve gene duplications, stably transmitted inherited germline gene replication that causes increased

protein expression and activity, or gene deletions that result in the complete lack of protein production. All of these mechanisms have been implicated in common germline pharmacogenetic polymorphisms. TPMT, thiopurine methyltransferase; ABCB1, the multidrug resistance transporter (P-glycoprotein); CYP, cytochrome P450; CBS, cystathionine -synthase; UGT, UDP-glucuronyl transferase; GST, glutathione-S-transferase.[11]

Metabolic enzymes in pharmaceogenomics

The cytochrome P450 (CYP) family of liver enzymes is responsible for breaking down more than 30 different classes of drugs. DNA variations in genes that code for these enzymes can influence their ability to metabolize certain drugs. [12] TPMT (thiopurine methyltransferase) plays an important role in the chemotherapy treatment of common childhood leukemia by breaking down a class of therapeutic compounds called thiopurines. A small percentage of Caucasians have genetic variants that prevent them from producing an active form of this protein. As a result, thiopurines elevate to toxic levels in the patient because the inactive form of TMPT is unable to break down the drug. Today, doctors can use a genetic test to screen patients for this deficiency, and the TPMT activity is monitored to determine appropriate thiopurine dosage levels [13].

[14] Table 1: DNA based biomarkers of enzyme activities considered as valid biomarkers [15]

Enzyme	Model drugs	Outcome measures	Study results	Ref
CYP2C9	**Warfarin**	**Maintenance dose Time to reach stable dosing**	**Patients with ∗2 and ∗3 maintained with lower doses and took longer time to reach stable dosing**	**17, 18**
CYP2C19	**Proton pump inhibitors**	**Plasma levels Gastric pH Gastroesophageal reflux disease cure rate**	**Higher in PM (20 mg) Higher dose (40 mg) showed no difference**	**19,20**
CYP2D6	**Codeine**	**Morphine formation Analgesic effects**	**Higher in**	**21**
	Atomoxetine	**Pharmacokinetic measure**	**PM higher AUC (10-fold)**	
UGT1A1	**Irinotecan**	**Grade 3/4 neutropenia**	**UGT1A1 7/7and 6/7 more frequent than 6/6**	**23,24**
		Pharmacokinetic parameters (AUC ratio of SN38G/SN38)	**UGT1A1∗28 and ∗6 with reduce ratios**	**25,26**
TPMT	**6-MP**	**Dose-limiting hematopoietic toxicity**	**More in TPMT deficiency or heterozygosity**	**27, 28, 29**

***Note*: UGT 1A1: uridine diphosphate glucuronosyl transferase 1A1; TPMT: thiopurine methyl transferase; SN-38: an active metabolite of ironotecan: SN-38G: a glucuronide metabolite of SN-38.**

CONCLUSION

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. Thus, the new science of pharmacotherapy is the treatment of patients based on genetic analysis for the diagnosis and classification of diseases. We must conclude that we now have a multitude of opportunities in delivering drugs to patients with the challenges of pursuing many new targets and the subsetting of these targets as a result of patient stratification. In the above review we discussed about the therapy and strategies regarding pharmacogenomics. In near future this may prove one of the most acceptable and useful means for the treatment of various diseases. The drug according to human genetics and historical evidence of patient will surely provide the rationale and individual patient therapy.

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