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STUDY AND REVIEW OF ROLE OF PHARMACOGENOMICS IN NEW DRUG DISCOVERY

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Abstract: *Drug development can be facilitated by genetic and genomic knowledge. Pharmacogenomics is the branch of pharmacology which 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. It aims to develop rational means to optimize drug therapy, with respect to the patient's genotype, to ensure maximum efficacy with minimal adverse effects. Pharmacogenomics is the whole genome application of pharmacogenetics, which examines the single gene interactions with drugs. Here, we review the contribution of genomics for understanding the biological relevance of a drug target, such approaches promise the advent of 'personalized medicine', in which drugs and drug combinations are optimized for each individual's unique genetic makeup.*

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INTRODUCTION:

For over 20 years, genomics has been used as a tool for accelerating drug development. Various conceptual approaches and techniques assist target identification, target prioritization and tractability, as well as the prediction of outcomes from pharmacological perturbations [1]. These basic premises are now supported by a rapid expansion of population genomics initiatives (sequencing or genotyping of hundreds of thousands of individuals), in-depth understanding of disease and drug perturbation at the tissue and single-cell level as measured by transcriptome analysis, and by the capacity to screen for loss of function or activation of genes. The aim of this work is to present progress in the implementation of genomics in drug development. Any such effort of course represents a snapshot in time, as technologies are being brought to bear on the problem of diagnosis and treatment of human disease at an amazing rate.

Old technologies may fade entirely if they become obsolete or may be retained for a specific use for which the technology remains well suited. As new technologies develop, they bring not only their unique contributions, but also provide opportunities for linking the new with the old to the benefit of both. Without knowing all of the genes involved in drug response, scientists have found it difficult to develop genetic tests that could predict a person's response to a particular drug [1]. Once scientists discovered that people's genes show small variations (or changes) in their nucleotide (DNA base) content, all of that changed: genetic testing for predicting drug response is now possible. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms [2]. The most common variations in the human genome are called single nucleotide polymorphisms (SNPs).

One important outgrowth of molecular medicine is the development of technologies for the transfer of therapeutic genes to cells in culture and tissues Molecular genetics reached human genetics *in vivo*, with potential applications both to medical about 1976, when the first human genes were research and the practice of clinical medicine. The cloned Transgenic methods, 'knock-outs' and use of genomic databases to find new targets for 'knock-ins' began in about 1986, and in about 1996, drug discovery and the rapid accumulation of human database searching became a fruitful way to do gene sequences is promising for clinical medicine, genomic research. The term 'genome' refers to an if the molecular level can be translated into improved organism's complete set of genes and chromosomes.

RELATED WORK

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyse in the 1970-1980s. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) [3] over beer at a meeting held in Maryland on the mapping of the human genome in 1986. In 1972,[4] Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein. In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA. The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ-X174 (5,368 bp), sequenced by Frederick Sanger in 1977. [5]

The first free-living organism to be sequenced was that of Haemophilus influenzae in 1995, and since then genomes are being sequenced at a rapid pace. A rough draft of the human genome was completed by the Human Genome Project in early 2001[6], creating much fanfare. As of September 2007, the complete sequence was known of about 1879 viruses, 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as Haemophilus influenzae. Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms.[7]

GENOMICS

Genome analysis may be divided into structural and functional genomics. Structural genomics is an initial phase of genome analysis, and has a clear endpoint which is the construction of high-resolution genetic, physical, and transcript maps of an organism [20]. This approach focuses on understanding how genotype variation gives rise to phenotypic variation, relying on physical and genetic maps and easily-typed DNA sequence polymorphisms. The expression approach (functional genomics) relies on the large collection of partially-sequenced cDNA clones. The benefits of the information arising from the accumulation of human gene sequences includes developing system atic ways of finding genes of interest, and their functions; hence 'functional

genomics'. The genes cloned and their corresponding DNA sequences provide the tools for comprehensive characterization of the expression patterns of this entire set of genes, and for systematic experimental investigations of the functional properties of their products. Thus, functional genomics, which represents a new phase of genome analysis, makes use of the structural genomics information. The investigation is primarily a systematic approach to elucidate the genome and its functions.[21]

The fact that most diseases do not follow a simple inheritance patterns has led to a significant challenge in the genetic dissection of the complex traits of diseases such hypertension, Alzheimer's disease, schizophrenia and diabetes.5 Four major approaches have been developed: linkage analysis, allele-sharing methods, association studies in human populations, and polygenic analysis of experimental crosses in model organisms such as mouse and rat. If these genetic approaches are successful, they have significant relevance in drug research

PHARMACOGENOMICS

Adverse Drug Reaction [20] conveys little of the horror of a severe negative reaction to a prescribed drug. But such negative reactions can nonetheless occur. A 1998 study of hospitalized patients published in the Journal of the American Medical Association reported that in 1994, adverse drug reactions accounted for more than 2.2 million serious cases and over 100,000 deaths, making adverse drug reactions (ADRs) one of the leading causes of hospitalization and death in the United States. For instance, the daily doses required to treat patients vary by 20-fold for the warfarin, by 40-fold for the antihypertensive drug propranolol and by 60-fold for L-dopa for parkinson's disease. Other drugs have clinical utility in a subset of patients with given pathology, e.g., antipsychotics that are ineffective in 30% of schizophrenics, suggesting that such drugs are only effective in patients with specific disease.[9]

Many of the deaths could be avoided if the physician had prior knowledge of patient's genetic profile, which determines the drug response. Currently, there is no simple way to determine whether people will respond well, badly, or not at all to a medication; therefore, pharmaceutical companies are limited to developing drugs using a 'one size fits all' system This system allows for the development of drugs to which the 'average' patient will respond. But, as the statistics above show, one size does not fit all, sometimes with devastating results. What is needed is a way to solve the problem of ADRs before they happen. The solution is in sight though, and it is called pharmacogenomics. Pharmacogenomics eventually can lead to an overall decrease in the cost of health care because of 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 is on medication; the number of medications patients must take to find an effective therapy; the effects of a disease on the body (throughearly detection).

Pharmacogenomics has its roots in pharmacogenetics. Whereas pharmacogenetics is the study of the linkage between an individual's genotype and that individual's ability to metabolize a foreign compound, pharmacogenomics is quite broad in scope, and is similar to molecular medicine, aiming to detect, monitor and treat the molecular causes of disease.[10]

Pharmacogenomics involves the application of genomics technologies such as gene sequencing statistical genetics and gene expression analysis to drugs in clinical development and trials. Since many diseases develop as a result of a network of genes failing to perform correctly, pharmacogenomics can identify the genes or loci which are involved in determining the responsiveness to a given drug. In this way, genetic characterization of patient populations is becoming an integral part of the drug discovery and development process. Pharmacogenomics may aim to capitalize on these new molecular insights to discover new therapeutic targets and interventions and to elucidate the constellation of genes that determine the efficacy and toxicity of specific medications [11].

IMPACT ON NEW DRUG DISCOVERY

Applying pharmacogenomics in the preclinical setting, one may start screening compounds with the least variation across individuals. If the target gene is selected, the compound that works best overall against all its subtypes may be chosen. Thus, drug selection is substituted for patient selection, decreasing the uncertainties that patient stratification introduces at the FDA and in marketing, as well as the need for a genetic screening. Genomics may also be used to select out adverse effects before drugs enter the clinic. For example, the gene-expression pattern for the liver of an animal administered a drug can indicate whether gene pathways related to toxicity have been turned on. Variations in gene expression levels may prove just as useful as genetic variation in predicting drug response at any stage in the clinic and as a diagnostic. Pharmacogenetic data are vital during the development of a compound with a narrow therapeutic index or which is metabolized

from a prodrug, as such information may influence decision of whether to discontinue development or design trials to study clinical responses in individual polymorphic for the relevant enzyme.[20]

Significant issues at the preclinical level usually need to be addressed. Problems of medicinal chemistry, developing drugs with the appropriate absorption, metabolism, distribution, and elimination profiles still have an empirical basis. Nonetheless, small molecule drugs directed toward targets discovered by genomics may soon account for a great majority of drugs introduced into the marketplace.[13]

Pharmacogenomics may benefit many stages of clinical drug development. It will significantly affect trial design, primarily through improved inclusion exclusion criteria and more effective assessment of patient responses. Genes linked with drug metaboldiseasesm in preclinical studies could be genotyped in patients recruited for phase I trials. Any genotype that correlates with adverse effects could then be used to screen out relevant patients in subsequent trials. Furthermore, if efficacy data are collected during phase I trials, polymorphisms in the drug target gene could be typed in phase I participants to assess whether they are linked with side-effects or with variations in drug response. That analysis could obviously be further refined in phase II trials, enabling companies to undertake phase III trials in a subgroup of patients that responds well and exhibits fewer side-effects. The resultant drugs would be expected not only to have better efficacy, but also a better safety profile[14]

At the clinical level, while the disease symptoms might appear to be uniform, individual-to-individual variations in these polygenic networks may make drugs healing for certain individuals while toxic for others. Pharmacogenomics can sometimes correlate gene variations with differential responses to the gene variations with differential responses to the same drug leads, thereby hoping to accelerate novel drug discovery dramatically, by defining specific populations that will benefit from a drug. While this approach may maximize the medical utility of existing pharmaceuticals, it could also rescue dead drugs. Several products that have failed in recent years in late stage clinical trials may on retrospective analysis be effective in subsets of patients, although at the time, there was no clear way of recognizing such subsets clinically. A study of the genetic differ ences between the individuals could provide answer. Consequently, traditional approaches that focus on broad groups of patients with a diagnosis (e.g. Alzheimer's disease) may need to be much more precisely divided into subsets of patients who may have a traditionally defined disease amenable to treatment based on a particular molecular target [15]

BENEFITS OF PHARMACOGENOMICS IN NEW DRUG DISCOVERY

Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms [16]. Following is the benefits.

a) Powered Medicines

Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases.[17] This accuracy will not only maximize therapeutic effects but also decrease damage to nearby healthy cells.

b) First time safety in drugs

Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyse a patient's genetic profile and prescribe the best available drug therapy from the beginning. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety as the likelihood of adverse reactions is eliminated.

c) Accuracy in determining correct drug dosage

Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics; how well the body processes the medicine and the time it takes to metabolize it. This will maximize the therapy's value and decrease the likelihood of overdose.

d) Prior screening of disease

Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage to maximize their therapy.[19]

e) 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. They will be inexpensive, stable, easy to store, and capable

of being engineered to carry several strains of a pathogen at once.

f) Easy Approval process of new drugs

Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. The drug approval process should be facilitated as trials are targeted for specific genetic population groups and providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.[18]

g) Low cost 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 care[20]

CONCLUSION:

Pharmacogenomics in pharmaceutical industry is a potential tool, awaiting use for the maximum benefit. It represents a radical advance in medical history. The main aims of it are; personalized therapy, improvement in efficacy and reduction in adverse drug reactions, correlation of genotype with clinical genotype, identification of novel targets for new drugs, and pharmacogenetic profiling of patients to predict disease susceptibility and drug response. Gradual inclusion of pharmacogenomic studies in drug discovery and development will cause substantial reduction in the expenses involved in drug development, ensure a safe clinical trial and reduce failures.

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