Chapter 10
Pharmacogenomics Genome Wise Association Clinical Studies

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ABSTRACT

Pharmacogenomics deals with drug responses in individual based on genetic variation in genome. Based on genetic variations, drugs may produce more or less therapeutic effect, and same way in side effects also. Physicians can use information about your genetic makeup to choose those drugs and drug doses to get better therapy. Optimizing drug therapy and rational dose adjustment with respect to genetic makeup will maximize drug efficacy and minimal adverse effects. This broken traditional 'trial and error' method of 'one drug fits all', and 'one dose fits all' which contributing to 25–50% of drug toxicity or treatment failures. This will contribute to improve the ways in which existing drugs are used, genomic research will lead to drug development to produce new drugs that are highly effective without serious side effects. This approach to bring personalized medicine more practice and drug combinations are optimized for each individual' genetic makeup.

INTRODUCTION

Human genetic profiling can be done by microarray expression, human SNP arrays and whole genome variants determination by using next generation sequencing technology. Whole genome wide screening approach enables better understanding about genetic profile, and provides possibility to check efficacy design for any animal experimental design. These technologies are made available to simultaneously monitor many cellular transcripts in parallel allows that result in more complete analysis of complex disease states and prediction of therapeutic response. Applications ranging from expression profiling to SNP genotyping, microarray gene expression in oncology are revolutionized with more clinical support to ensure better analysis of role of genetics in drug response.

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Allelic variation in individual genotype also provides phenotypic relation, like intermediate, ultra-rapid, non-response categories of CYPgenes metabolizer etc. Several genetic events influence a same phenotypic trait, therefore, establishing genotype-to-phenotype relationships can be far from consensual with many enzymatic patterns. Many genes involved in pharmacokinetics process have been described as being highly polymorphic. Genes likes DPD, UGT1A1, TPMT, CDA involved in the pharmacokinetics of 5-FU/capecitabine, irinotecan, 6-mercaptopurine and gemcitabine/cytarabine, respectively. Patients affected by these genetic polymorphisms will experience severe/lethal toxicities upon drug intake, and that pre-therapeutic screening does help to reduce the risk of treatment-related toxicities through adaptive dosing strategies (Evans & Relling, 1999).

Drug adverse effects vary from patient to patient as well as disease to disease. Drug response characteristics are very complex and depends on profound gene-drug interactions. For drugs that have a narrow therapeutic index caused by inactivation of certain polymorphic drug-metabolizing enzyme and expected to have an increased risk of adverse drug reactions. Some drugs require a metabolic activation by polymorphic drug- metabolizing enzyme (for example, codeine) low therapeutic efficacy or treatment failure. For many drugs that have a broad therapeutic window caused by genetic variants which leads to impaired drug metabolism.

Pharmacogenomics researchers have already identified many genes whose variations affect drug responses. They also know where to look for the numerous others they are bound to discover in the future. Pharmacogenomics tests are used to identify the patients are most likely to respond to certain cancer drugs, tests provide tools for physicians to better manage medication selection and side effect amelioration. Pharmacogenomics is also known as companion diagnostics, meaning tests being bundled with drugs. Examples include KRAS test with cetuximab and EGFR test with gefitinib. Beside efficacy, germline pharmacogenetics can help to identify patients likely to undergo severe toxicities when given cytotoxics showing impaired detoxification in relation with genetic polymorphism like canonical 5-FU.

All drugs cannot be personalized, clinical significance in tailored medicine for prodrugs, drugs with a narrow therapeutic index and drugs that target a key molecule or a critical pathway. Drug safety is the first arena in which patients can benefit from pharmacogenetics and pharmacogenomics. Tumor responses to the inhibitors of oncogenic tyrosine kinases are associated with the presence of activating mutations within the genes encoding the target kinases, targeted cancer therapy is thus a promising individualized drug therapy. The U.S. Food and Drug Administration (FDA) recommends genetic testing for certain chemotherapy drugs like mercaptopurine (Purinethol) to patients with acute lymphoblastic leukemia. Some people have a genetic variant that interferes with their ability to process the drug. This processing problem can cause severe side effects and increase risk of infection, unless the standard dose is adjusted according to the patient's genetic makeup.

Using microarray, cellular transcripts expression in disease states and after treatment to identify drug response at molecular level. Microarray is either silicon chip or glass slide contain series of immobilized complementary DNA molecules or oligonucleotide probes. Targeted DNA labelled with a fluorescent, transcripts abundance based on amount of hybridized labelled dye on each microarray. Each gene represented by a probe set with 11-12 pairs of oligos composed of 25 nucleotides. This approach would make it possible to consider the measured intensities as a proxy for actual mRNA concentration. The scanner produce DAT file is the intensity for each pixel on the array and CEL file, which is the summary of probe intensity for every probe on the array. An expression file, which is the Affymetrix Suite compilation of the probes into gene expression values. An intensity of each probes are corrected