EDITORIAL

Pharmacogenomics in Therapeutics

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Pharmacogenomics is the branch of pharmacology that involves the study of drug response with the entire compliment of genes; the other closely related term ***Pharmacogenetics***, refers to study of drug response with a relatively restricted number of genes (1) but both terms are used interchangeably.

The genes code for metabolizing enzymes, transporters and/or receptors. Therefore, the genetic traits affect drug pharmacokinetics and pharmacodynamics (2). Similarly, the genetic variants of the major histocompatability complex (MHC) can affect the expression of human leukocyte antigen (HLA) allele thus affecting the drug safety (3). A defect at any level can result in treatment failure and serious adverse drug reactions (ADRs) due to generation of toxic metabolite or accumulation of the substrates, thereby can affect the treatment. These genetic mutations or polymorphisms include single nucleotide polymorphisms (SNPs); insertion and deletions (indels), copy number variants (CNV); substitutions; inversions; translocations and conversions dispersed throughout the genome reported in the literature (1).

The current focus of Pharmacogenomics is to develop personalized medicine i.e. tailor made medical treatment for each patient (4). Once the candidate gene responsible for drug effects is known, subjects can be screened for polymorphism and literature review will guide the therapeutic decision. Thus polymorphisms act as a marker for drug safety based on the genetic information of recipient shifting pharmacogenomics from the bench to bedside.

HLA-B*1502 has an association with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in South Asian Indians when exposed to carbamazepine (5).Hence, it makes sense to screen all the patients requiring carbamazepine for epilepsy or other indication for HLA-B*1502 allele. This can help in risk prediction and safer drug prescription for patients (6).

The defective metabolizing enzymes can increase the risk of ADRs due to drug accumulation. The anticancer drug irinotecan (topoisomerase1 inhibitor) is sequentially activated to active metabolite followed by uridine diphosphate glucronosyltransferase 1A1 (UGT1A1) mediated inactivation. The additional TA repeat of UGTA1A1 results in less glucuronidation of active metabolite.This UGT1A1 homozygous or heterozygous polymorphism, cause severe diarrhea and neutropenia as compared to normal subjects.The myelotoxicity to irinotecan can be minimized by testing for genetically defective allele and using a lower starting dose or substituting another safe and effective drug in subjects homozygous for defective allele but the heterozygous patients tend to tolerate a normal starting dose of irinotecan and show variable results clinically (7).

A single SNP or CNV may not always explain the event completely as gene expression may be controlled by multiple genes. Hence, whole Genome Wide Association (GWA) studies rather than candidate gene analysis has improved the understanding many complex traits (8).

Warfarin, an oral anticoagulant, has a narrow therapeutic window resulting in serious consequences like

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stroke and myocardial infarction at one end and bleeding to death at another. The genetic variations in drug target vitamin K epoxide reductase complex1 (VKROC1) and metabolizing enzyme Cytochrome P4502C9 (CYP2C9) increase the bleeding risk and hence a lesser dose requirement (9) in Caucasian and Asian patients. The variation attributable to VKORC1 gene polymorphism is 30%; both VKORC1 and CYP2C9 is 40% and increases to 55% when other variables are also considered (10).

The genomic tool helps to select patients for highly effective and expensive treatment with maximum benefit (11). Trastuzumab having very good efficacy against Her2 receptor variants in breast cancer must be used for patients positive for Her2 variants (12). Similarly, Maraviroc, CCR5 blocker, has better virological control and maximum efficacy (2-3 log reduction in viral load) (10) when used in CCR5-tropic HIV-1positive patients (13).

There are many environmental variables like dietary habits, diet, gender, age, lifestyle and level of health which can affect drug response but the key appears to be the unique, individual genetic makeup. The GWA studies are able to explain small variations and thus refine the personalized medicine used in diagnostics, therapeutic optimization and even prognostication (8). The only drawback is the cost, which is coming down with the development of newer techniques and assay methods.

Pharmacogenomic testing is worth the price as it identifies the patients at high risk of ADRs as well as those likely to get the maximum benefit from a particular drug. Food and Drug Administration recommends inclusion of pharmacogenomic markers for data collection as predictors of drug safety and efficacy in clinical trials (6). In India, the Department of Biotechnology has taken initiative to develop Pharamcogenomics.

Pharmacogenomic testing improves drug safety by complimenting therapeutic drug monitoring as it accounts for pharmacodynamic variability and helps in safe prescription of drugs. Thus pharmacogenomics aids personalized medicine in true sense.

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