LETTER TO THE EDITOR

Concept of Pharmacogenomics and Future Considerations

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Conceptually, pharmacogenomics is the study that aims to identify impact of an individual's genetic architecture on drug response. Logically, the study can be applied by discovering the associated genes, their underlying mechanism, and functional interpretation followed by clinical implementation in the form of diagnostic models or recommendations for drug dosing.

Accumulated literature provides evidences for association of genetic variants with disease and drug response that builds upon the pyramid of pharmacogenomic knowledge (Figure 1). Basic laboratory research applying candidate gene and genome-wide approaches constitute the base of the pyramid and indicate that genetic variability majorly contributes to differential therapeutic outcome [1–3]. Evidences related to functional biological consequences of identified variant constitute the next level of pyramid. The function can be elucidated by studying transcript and protein profile of genetic loci through *in vitro* cell- and *in vivo* animal model-based methods. Once function is determined experimentally, it may be further validated by conducting large-scale human population-based studies for establishing its physiological role. Depending upon the frequency of exposure variable and outcome of interest, associated ethical issues, and resources available to the researcher, one may design case control, cohort, or randomized clinical trial. However, conducting a prospective study is more fruitful as it helps to map the trajectory of neuropsychiatric/neurological disease by developing a clear understanding of disease pathophysiology and therapeutic outcome at different phases of treatment. Furthermore, these evidences are then statistically interrogated through meta-analysis considered to be at the top of the pyramid of evidence prior to its clinical implementation. The incorporation of this genetic data in routine clinical practice could ultimately lead to more accurate patient profiling and treatment optimization which may further facilitate identification of patients who are predisposed to adverse drug reactions (ADRs) including

drug-induced toxicity or inadequate response. One of the classical example of the application of pharmacogenetic studies is the Food Drug Administration (FDA) recommendation for testing HLA-B*1502 in patients of Asian ancestry before initiating treatment with carbamazepine [4]. The basis of this recommendation originated from series of case-control studies showing role of this genetic variant in skin reactions. The results have now been confirmed by a prospective study as well as meta-analysis showing a pooled odds ratio of 116 [5].

Recently, genetic studies of brain diseases have gained considerable attention because of hit and trial method of treatment initiation further adding to variable drug response and ADRs leading to poor adherence and high relapse rate. Although substantial genetic data is now available for drug response (e.g., ABC transporters in epilepsy, dopamine and serotonin receptors in schizophrenia) and disease susceptibility (ion channels in epilepsy and *APOE* in AD) for several of these brain disorders, however, majority of the findings have not translated into FDA recommendations. This could be due to poor replicability coupled with lack of integrative approach including failure to incorporate data on dose and drug levels. Nevertheless, few drugs have managed to get FDAs approval as genetic information has been included in respective labels. Nowadays, these genetic tests are used in routine clinical practice across the world. For instance, genotyping of *HLA-DQB1* is recommended for prescribing optimal clozapine (antipsychotic) dose, and information on *CYP2D6* variants has also been included in labels of several antipsychotics and venlafaxine (antidepressant) [6]. Our data indicate that both clinical parameters and genetic markers are important decisive factors for predicting drug response in epileptic and schizophrenic patients [1,2]. Consistent with the next step in knowledge pyramid, we are also in the process of elucidating the functional role of identified markers with unknown functions in relevant cell lines and animal models to

Figure 1 Logical levels for applying pharmacogenomics.

strengthen the potential for their clinical utility. Simultaneously, we have also collected data on drug doses, drug levels, and side effects to validate FDA recommendations in ethnically diverse Indian population.

Limitations of Pharmacogenomic Studies

One of the major limitations of the pharmacogenomics research is its study design. It has always been unethical to give placebo or inferior treatment to diseased individuals in the presence of better available therapeutic options. In this direction, validation of genetic data in clinical trials may be much more difficult with limited experimental data and lower predictive performance of the genetic markers in laboratory-based studies [7]. Nonreplicability of detected associations is another major limitation of pharmacogenomic studies. This requires an independent study with the same treatment type in ethnically similar population showing related reference ranges for therapeutic dose and drug levels and homogeneous phenotypes. Other than these, comorbid conditions, concomitant therapy, and follow-up duration are critical issues that need to be taken into consideration before conducting a pharmacogenomic study [8]. Unpublished negative findings and experimental studies further append the list of limitations. Negative results may not reflect the false hypothesis; rather, it may be due to phenotypic heterogeneity, inappropriate statistical analysis, or due to affinity of drug for its off-target, which unexpectedly disrupts the signaling, resulting in inadequate drug response [9]. Small sample size of pharmacogenomics traits is another major issue of concern. To achieve adequate sample size, inclusion of multiple centers is required. But this could introduce considerable heterogeneity at clinical as well as genetic level [8]. Lack of pharmacokinetic parameters is another limitation, which if incorporated would also provide understanding of the variable therapeutic drug levels, drug doses and drug-induced toxicity. Recently, researchers have started adopting an integrated approach where they not only identify genetic variants, but also simultaneously screen serum drug levels and respective metabolites, and drug doses, and biochemical parameters in patients at

the time of enrollment and at each successive follow-up as well. The correlation of pharmacokinetic parameters and pharmacodynamic pathway variants with therapeutic outcome and development of ADRs may help us to find out the underlying metabolizing pathway and its role in the drug response.

Future Considerations

Huge accumulating data from *in vitro* and *in vivo* studies provide evidence to understand the impact of genetic manipulation of genes involved in drug kinetics and action. Tissue-specific RNA expression analysis of the individuals who participate in clinical trials, during early phases of drug development (for marketed drugs also), may provide better evidence about the drug mechanisms, affected biological pathways, and hence enhance prediction of drug response [10]. Although non availability of brain samples hinders the gene expression analysis, the leukocytes could serve as surrogate samples. A recent report observed higher baseline mRNA transcript levels of IL- β , TNF- α , and macrophage inhibiting factor (MIF) in nonresponders and reduced IL-6 expression responders on antidepressant treatment, suggesting these genes as potential biomarkers [11]. Furthermore, differential drug dose-based expression studies in various cell lines may provide profiles of involved genes and thus serve as surrogates for individuals where cellular conditions can be compared with individual's response [12]. In addition to this, cheminformatics has also recently emerged as *in silico* tool that can perform screening of molecules and drug-protein interaction. Cheminformatics reduces the number of compounds in initial screening by predicting best fit molecule for particular target using docking method and repositioning of drugs already in the market. These can be further validated by various biochemical assays. Selected molecules can be investigated with wide range of targets that provide information related to interaction with their off-targets, which may help us to understand the mechanism of ADRs [13,14]. Kinnings et al. [15] used a novel computational strategy and predicted binding of COMT inhibitors (entacapone and tolcapone, used to treat Parkinson's disease) to

InhA enzyme considered essential for type-II fatty acid biosynthesis in the synthesis of the bacterial cell wall. This was further validated by *in vitro* assay that confirmed its potential as lead compounds against drug-resistant strains of *Mycobacterium tuberculosis*. The approach used also reduces the time and cost of clinical trials of ongoing and upcoming molecules. Application of pharmacogenomics data therefore can help clinicians in treatment initiation and drug prescribing, drug dosing, and prediction of ADRs. Most of the medicines have been discovered by serendipitous observations, whereas currently prescribed drugs are analogues and their mechanism is poorly understood; thus, new genetic information-based drugs may help in personalized medicine and drug development.

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Conflict of Interests

The authors declare no conflict of interests.