The Emerging Focus on Pharmacogenomics

Abstract

Drugs are designed to treat medical conditions for the general population. Idiosyncratic reactions to drugs are determined by the individual's respective genetic variations that direct effectiveness and side effects. Adverse drug reactions rank within the top ten leading causes of death in the developed world. The field of pharmacogenomics has advanced in the last fifty years, picking up significant momentum with recent biotechnological developments that allow scientists to investigate the human genome and provide individualized drug therapy that will increase the efficacy of drugs and decrease the incidence of adverse drug reactions. Pharmacogenomics has reached a milestone in making personalized medicine accessible and effective. The medical community shares this responsibility for the emerging focus on pharmacogenomics with regulatory agencies and bioinformatics specialists as they struggle to streamline vast libraries of information and reconcile public and regulatory approval on this critical path to the next level of health care.

Keywords: Pharmacogenomics, Bioinformatics, alleviate adverse drug reactions (ADRs) and biochips.

Introduction

Pharmacogenomics is a tool for therapy optimization, used to elucidate the interrelationships between individual sequence variation and differential responses to drugs. Ross (2017) investigated the need for using pharmacogenomics to alleviate adverse drug reactions (ADR) such as rheumatoid arthritis with emphasis on children. Stearns, Davidson and Flockhart have successfully applied pharmacogenomics in the diagnosis, and tracking prognosis in the development of customized treatments for breast cancer patients (2004). By having the entire genomic sequences available, this will have an effect on new drug targets and antigenic determinants for vaccine development and this could improve diagnostics via the identification of unique sequences. Antibiotic resistance is an ever increasing problem in our medical society. Mary Hayney's research stresses on the importance of capturing the genome of the pathogen as well as the host, with the focus on the susceptible gene and strategizing drug targets (2002).

Biotechnological inventions and advances have contributed ultra-high-throughput sequencing, biochips, and microarray-based genomic selection (Nebert & Vesell (2008). Hardiman's work at UCSD is playing a significant role in this post-genomic era through the development of

protocols, with a focus on complex brain chemistry (2012). Chan & Comabella (2011) call out an urgent need for the development of biomarkers to identify the benefit and the risk to the individual patient. In spite of concrete links between genetics and drug metabolism/reaction there is little evidence of clinical implementation. To overcome this bottle neck, Clinical pharmacogenomics implementation consortium (CPIC) of the National institutes of health's pharmacogenomics research network and the Pharmacogenomics knowledge base provides current, peer-reviewed, online guidelines for gene/drug pairs. The guidelines contain critical information for clinical implementation like indications for testing, tables summarizing relevant functional variants, relationships of variants to derived diplotypes and likely phenotypes and recommendations regarding drug dosing and drug choice based on phenotype. There remains a significant clinical evidence gap between companion diagnostic tests and the pharmacogenomics of personalized medicine in the pursuit of the ideal therapeutic drug. Cohen stresses the need for proof for policy to achieve the cost-effectiveness of pharmacogenomics. The 10% of all FDA approved drugs have pharmacogenomics data associated with it. The solution proposed is to coordinate reimbursement with clinical testing. (2012).

Studies linking different population to adverse drug reaction are in its infancy. These pharmacoepidemiological studies taken from statistics of inpatients, outpatients and emergency patients roughly categorize them into type A (ADRs that are dose dependent and predictable) and type B (ADR that are dose independent and non-predictable) reactions comprising 80% and 20% of all studied ADRs respectively (Thong, Teck-Choon, 2011). Determining risk factors and appropriate genetic testing is recommended to overcome estimated 3 million incorrect or ineffective drug prescriptions annually (NIH – SACGHS, 2012). There are drug related factors that are dependent on methods of administration of drugs and its ability to act. Host related factors depend on age, sex, concomitant diseases and especially ethnicity and genetics. Adults and mostly females are observed to be affected by ADR. Increasing interest in drug derived antigen plays a key role in the development of drug hypersensitivity to avoid severe cutaneous drug reaction (SCAR) like Steven-Johnsons syndrome (Thong & Teck-Choon, 2011).

Most methods by which investigators evaluate the outcomes of a complex disease are too simplistic. According to Nerbert et al (2008), the ongoing and continuous discoveries bring new surprises about our genome and in addition constant questioning reviews whether the personalized medicine is almost here or that individualized drug therapy will soon be a reality has been at utmost radar. Nerbert et al (2008) summarized in their research as an "unequivocal genotype" or even an "unequivocal phenotype" is virtually impossible to achieve with current limited-size studies of human populations and the solution and presents are to divide a large population into more valuable subsets, that can not only enhance the statistical power of a study, but at the same time reduce the number of individual millions of dollars' costly clinical trials.

Methodology

The virulence of the pathogen and the susceptibility of the host is where the development of infection is influenced by and thus animal models with controlled environment and exposure are used in research to determine immunological response to infections (Oliver & Williams-Jones, 2011). There are many genes whose function in the human genome is still unknown. Identifying polymorphisms associated which such genes called candidate genes becomes restricted with limited knowledge. For patients who tend to show family history for certain diseases, investigators narrowing down the search for the gene of interest and determining co-segregation of micro-satellites and disease assists researchers tremendously. This candidate gene strategy and animal models continue to have been used in identifying a susceptibility gene for tuberculosis and leprosy(Oliver & Williams-Jones, 2011).

Identifying immunologically important peptides for cytotoxic T lymphocytes, known as CTL epitopes is significant to the immune response of a viral pathogen. The role of CTLs is to seek out virally infected cells by recognizing the peptides presented by human leukocyte antigen (HLA) glycoproteins on the cell surface and killing the infected cells, making them an ideal candidate gene. They are isolated using ELISA procedures. Furthermore, knowing the genomes of the infecting organisms can help in diagnosis since human immunodeficiency virus (HIV), hepatitis viruses and mycobacteria are just a few of the pathogens that can be identified from their genomic sequences. The traditional culturing and sensitivity testing of these organisms is now being replaced by the DNA fingerprinting for the detection and species identification of organisms (Hayney, 2002).

Ameen, Qadir & Ahmad (2012) in their article assert that mutations in RAS/MEK/ERK and P13K AKT-mTOR pathway is involved in pathogenesis of breast cancer and pharmacogenomics applications will lead to individualization of therapy, and this is a complete contrast to in this day and age of clinical norms where drug affects are studied among large groups of patients regardless of their genetic based differences (2012). With the emerging focus in the field Pharmacogenomics, it can help by identifying molecular subtypes of disease, aid in discovery of new drug targets, and integrating genetics with other technologies such as transcriptomics, proteomics, metabolomics, imaging, PoP or PK/PD modeling.

Certain characteristics of the tumor such as tumor size, lymph node metastases and grade, all used to predict prognosis, but the genetic variants among each individual resides in the germline DNA of the patient, and with the help of pharmacogenomics, that is the use of genetics and genomics in drug discovery and development, response to specific drugs are said to be related to genetic inheritance of simple sequence length polymorphism (SSLP), single nucleotide polymorphism (SNPs) or insertion or deletions in important genes relevant to drug disposition and effect including drug metabolizing enzymes, transporters or drug targets.

Ross (2007) investigates the need for using pharmacogenomics as a means to mitigate adverse drug reactions (ADRs), with a focus on autoimmune diseases such as rheumatoid arthritis, with an emphasis on children. We learn that as of 2007, ADRs are among the leading causes of death in the most advanced countries in the world, and require annual medical costs up to $177B in the United States. Genetic elements account for up to 95% of the variances in drug response, including ADRs. (2007). There are many drugs that should be administered at different doses to patients that possess the genetic variations that cause ADRs, such as administering codeine to treat post-natal maternal pain, warfarin therapy as an anticoagulant, and azathioprine treatment for autoimmune diseases. The FDA is moving forward by establishing pharmacogenomics guidelines for industry. The goal is to predict the polymorphisms that impact drug metabolism. Databases such as the International Hap-Map Project are providing public information to be shared and compared, which will facilitate the growth and possibilities for pharmacogenomics.

We must create a mechanism by which the clinical data is simultaneously shared among the researchers and clinicians to facilitate the process of bringing the drug to the patient. ClinicalTrials.gov is a clearinghouse for clinical trials that categorize studies according to clinical condition, drug intervention, sponsors, and location. It also provides information for investigators. The gap between clinical trials and publications presents a significant delay in bringing the drug to market. For example, in Figure 2, we see the lag involved in the investigation into how polymorphisms "influence the efficacy and side effect profiles of Paroxetine and Escitalopram for major depression treatments, a Phase IV clinical trial was launched and registered in ClinicalTrials.gov in 2006. (Figure 1). The trial was completed 4 years later in 2010" and was published soon thereafter (in press).

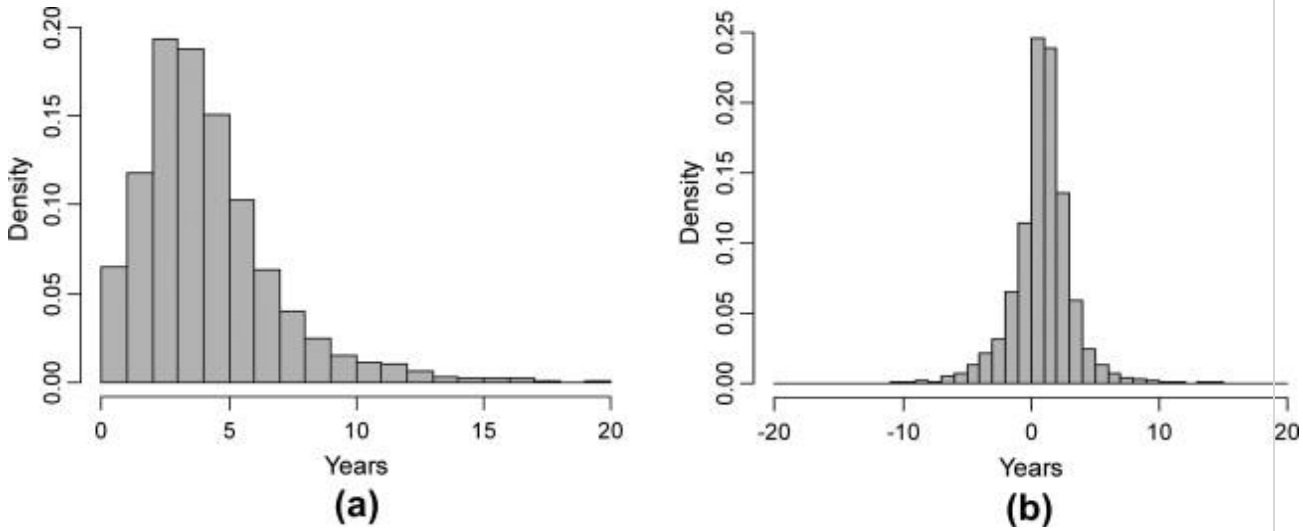

Figure 2. Time lag between clinical trials and publication (a) current average is five years (b) illustrates the density from the beginning of clinical trials to the market delivery.

It is critical that we merge our databases so that we can have full disclosure, consensus, and efficiency. Right now, as is evident in Figure 3, the gaps between the three major data agencies are significant.

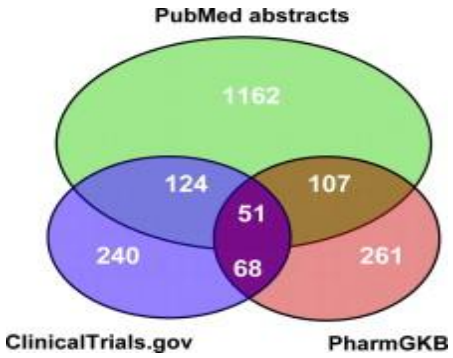

Figure 3

Figure 3. This shows the three largest pharmacogenomics data agencies and the limited overlap of information on the "comparison of gene–drug–disease relationships identified from different sources. A total of 240 relationships were found in ClinicalTrials.gov. 124 and 68 such relationships were found to be overlapping with 1162 results in PubMed and 261 results in PharmGKB, respectively. Fifty-one relationships were found in all three sources" (in press).

Currently researchers believe in multidisciplinary approach on a wide variety of therapeutic drugs. Understanding biological mechanisms through computational and experimental scientists is a key focus. Large clinical and translational studies of diverse population are being carried to understand membrane transporter proteins and the pharmacogenomics research. Animal models are used to figure out pathways to biologically relevant candidate genes. Computational models coupled with experimental assays are used to understand functional aspects of mutations. These computations assist in marking mutations with disease associations and neutral points which is further confirmed by experiments. Research into non-coding part of the genome and its influence in gene regulation is being explored. Connecting dots between diverse population and membrane transporter proteins with the help of variant animal models ina multidisciplinary level with robust technology is in the forefront of emerging focus on pharmacogenomics (Kroetz et al., 2009).

Conclusion

Pharmacogenomics advances enhance our ability to identify and establish biomarkers, diagnose, track prognosis, optimize drug therapy, personalize chemotherapy, and improve drug efficacy. Ultra-high-throughput sequencing, biochips, and microarrays as well as nanotechnologies bring us to the next level of science and clinical care. The international, standardization of technologies, protocols, and libraries will open up the field for collaborative, global health care as well as pin-pointed, personalized medicine. The goal is to make pharmacogenomics accessible

to all on the clinical stage. Sharing information proactively among researchers, clinical studies and clinical practice, government regulatory and approval agencies, drug developers, and drug manufacturers will give the necessary power to pharmacogenomics in our global society.

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