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The Advancements in Pharmacogenomics: A Comprehensive Review

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ABSTRACT

The term pharmacogenomics comes from the combination of the two words: pharmacology and genomics. The advancement in the field of genetics and wide amount of research in human genomics, the knowledge and acceptance of the stream of pharmacogenomics is humungous.Each miniscule details about the gene and customized drug delivery through precision medicine is possible.

KEYWORDS*: pharmacogenomics, genomics, pharmacology, genetics, precision medicine*

INTRODUCTION

Pharmacology is the study of how the drugs or medications work in the body and the stream genomics means, it is the study of how genes may act together to influence health, development or how the human body works. These changes or variation may be inherited.

Therefore, pharmacogenomics is the study of the genetic factors that influence how a drug works in the body. Factors that influence how the person responds to medication includes their external and internal environments, the overall health, as well as their genetic make-up.

The goal of the pharmacogenomics is to understand the role that a person's genetic make-up plays in how well a medicine works and functions in the human body, as well as what side effects are likely to happen. Understanding this can help tailor drugs for that person

(personalised medicine) or for a group of people(Lehti et al.,2018).

Many significant challenges remain in the field of the pharmacogenomics, beyond the simple identification of more genetic variants related to the drug response. First, the transition to whole-genome sequencing will require newer the analysis methods, as well as more extensive annotations, to assign meaning to the novel variants. A database of the relation between genes, variants, and drugs, such as the PharmGKB, will be instrumental in the aggregation of information curated from the literature. In addition, the characterization of the adverse events and their underlying causes is a topic of active research (Bolton et al.,2014).

Finally, the applications of pharmacogenomics to a clinical setting will require the education of the physicians in the utility of genome sequencing or precisely genotyping for the benefit of their patients. With the dawn of human genome sequencing, especially the impending widespread availability of personal genotyping to the public, and an expanded knowledge of the bioclinical impact of genetics and molecular biology, the physicians around the world are beginning to use patients' personal genetics in informing the prescription decisions. While still in its early phases, pharmacogenomics will undoubtedly pave the way in the development of personalized medicine.

DYNAMICS OF PHRMACOGENOMICS

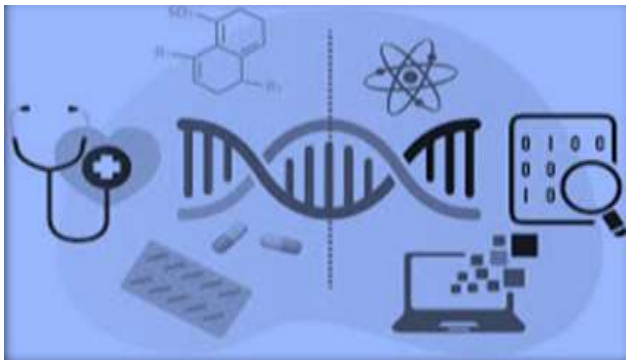

Figure: 1

When a physician administers a drug, an intricate and specific cascade of events unfolds as this molecule interacts with the physiological environments. In the simplest scenario, a drug (after interacting with a number of proteins (macromolecules) on its way to its target) may act as an agonist or an antagonist against a receptor, which is mainly composed of one or more

proteins. At the molecular level, the metabolite can bind to the protein's bioactive site, which can include ligand-binding sites, conformation-altering sites, or the catalytic sites. This effect can then be mainly propagated through biochemical pathways to produce a cellular and finally, the systemic physiological effect. Along the way, human genetic variation can affect the way these receptors interact with drugs, paving to consequences in the efficacy of the drug and causing potential adverse events (Yang et al.,2012).

PRINCIPLES OF PHARMACOGENOMICS

Pharmacogenomic Terminology, Nomenclature, and the Test Interpretation An understanding of pharmacogenomics requires a familiarity with the allied terminology, including general genetic terms. Pharmacogenomic alleles can be reported in a variety of ways, encompassing star allele nomenclature (e.g., TPMT*2), the nucleotide changes (e.g., rs1800462C>G [cytosine changed to guanine]), and the amino acid changes (e.g., p.A80P [alanine changed to proline])(Montano et al.,2018). Note that italics (e.g., CYP2D6) are availed when referring to the gene and that regular text (e.g., CYP2D6) is availed when referring to the protein. Information about how particular the pharmacogenomic alleles are defined can be found on the Pharmacogene Variation Consortium website.

Figure: 2

With the star allele nomenclature, the "wild-type" (i.e., normal, reference) sequence of an allele is mainly assigned *1. All other alleles are called by other numbers (e.g., *2, *3, *4), which are precisely assigned in the order each allele was discovered. For any given gene, an individual typically inherits the two copies – one maternal allele and one paternal allele. Certain genes, such as the CYP2D6, are susceptible to gene duplications, the multiplications, and deletions, making it possible to have more or less than two copies of this gene (Kamdem

et al.,2008). Therefore, the copy number variation is an essential component in interpreting pharmacogenomic test results for the CYP2D6. Without copy number variation, a phenotype cannot accurately be assigned. The combination of the alleles is what makes up a genotype (or the diplotype) result (e.g., TPMT*1/*2). For many pharmacogenes, each allele is assigned a function (e.g., aggrandized function, normal function, decreased function, no function). The combination of the functions of the inherited alleles determines a patient's phenotype (e.g.,the thiopurine methyltransferase [TPMT] intermediate metabolizer).

Certain genes (e.g., the CYP2D6, CYP2C9 and dihydropyrimidine dehydrogenase [DPYD]) use an activity score system to mainly translate genotype to phenotype whereby the particular alleles are assigned an activity value (e.g., 0 for no function alleles, 0.5 for the decreased function alleles, and 1 for normal function alleles), and the sum of the activity values for a particular diplotype corresponds to the particular phenotype (e.g., an bioactivity score of 2 for a CYP2D6 result translates to a normal metabolizer). The Clinical Pharmacogenetics Implementation Consortium (CPIC) mainly garners guidance on how to assign a phenotype from genotype for genes that are the subject of their clinical guidelines (Stanulla et al.,2000).

APPLICATION

Many common diseases having the high morbidity as well as mortality rates have now known with well-established genetic components (Meissner et al., 2004). The degree of the role of genetics has been predicted for the diseases like obesity and diabetes according to their sibling analysis. In the same way, some rare gene mutations can garner a vision into the more complex biological processes. For instance, when the mainly subject possesses extreme levels of HDL in their blood, one can easily demonstrated the influence of the CETP (cholesteryl ester transfer protein) on patients HDL levels. In another case, a person having the deactivating mutations due to the Januskinase 3 (JAK 3) gene shows much severe combination of immune-deficient syndromes, as sometimes inhibition of JAK3 was expected to affect the human immune suppression. Hence, this led to the new investigation on drugs having CETP inhibitionand JAK3 inhibition with the aid of the pharmacogenetics. Also, with the adventof pharmacogenomics, the path of relationships between the disease state and humangenes has now established which pave to the suitable selection of therapeutic targets.

Nowadays, many academic institutions and the Pharmaceutical companies aremoving toward the investigation on the relationship between the disease phenotypes and genetic variations to better categorize diseases (Marino et al., 2009) . Although the consortium of medical phenotypes having linkages with samples of DNA garners a promi-nent opportunity for examine the genetic variation which are present in patients (Anderer et al.,2000).

The Investigation of genetic variation can be done by collection of DNA of particular patient. This is mainly characterized in a study where DNA from a person involves in trails of the lipid lowering demonstrated a swift connection between phenotypic novellipase gene family and for the HDL levels. As per literature reports, above mentioned studies are based on the sound hypothesis which is linked to candidate's biologicalgene selection. Now it is easy to mainlycross-examine the genome selection which is solely depends on the phenotypic criteria .These stages have now substituted around300,000 SNPs across the genome, by exploiting only the few haplotype-defining SNPs.Perlegen sciences have developed very advanced genotyping technologies which has with a capability of genotyping mass hundreds or thousands of the markers with the help ofhigh-density based oligonucleotide arrays linked with the restriction enzyme-basedgenomic reduction.

However, as these technologies advances, still exact number of the haplotype-defining SNPs is uncertain. Some findings are recently reported relation to assess polymorphisms across selected gene regions recommends that, it is quiet necessary to reach an r2 of >0.8% in order to detect more than 80% of all haplotypes (Jamroziak et al.,2004). Due to the HapMap project progression with defined LD patterns linkage, scientist woring on the genes will thorough assess to the degree of LD in a represented regions or selected regions. This will mainly enable to explore more around selection of SNP regard-less design of study. As the genome, approach does not depend upon selection of candidate genes, so understanding on the complex diseases such as psychiatric or cardiovascular diseases will become more efficient.

Some researchers precisely believed that the new horizons on the LD coverage about insights of human genome and SNP density will show the perception of the substantial genomic portion areas and its relation with interest of the phenotype. To assess the Perlegen Sciences chip-based array-based platform and to justify the haplotype tagging approach for the identification of the genetic associations, 7283 SNPs connecting the 17.1 mega bases (Mb) of

DNA were geno typed for detecting linkages with HDL levels. Further, the SNPs were connected with 50 CETP haploblock gene were found out as the most valuable association in the dataset. The companies like Perlegen and project like Hap Map project recently declared their purpose to garner it SNPs markers into public provinces to further advent to basis for such kind of experiments which aid in the scientific community (Gregers et al.,2015).

History and initial inventions in pharmacology has the prime step in further advancement in this field (Dr. Sreeremya. S, 2024a). New age geneteic techniques like CRISPR (Dr. Sreeremya. S, 2024b) and other genomic tools has also made great impact in the field of pharmacology (Dr. Sreeremya. S, 2025a). Various streams of pharmacology like pediatric pharmacology (Dr. Sreeremya. S, 2019), precision medicine (Dr. Sreeremya. S, 2025b), community pharmacy is influenced by the inventions and research performed in the field of pharmacogenomics (Dr.Sreeremya.S, 2026).

IMPACT OF PHARMACOGENOMICS WITH AN EXAMPLE

Polymorphic variation in the UDP-glucuronosyltransferases Conjugation reactions such as glucuronidation mediated by the UDPglucuronosyltransferases (UGTs) are now also attracting increasing attention, especially in the field of oncology (Zalewski et al.,2008). The Glucuronidation is by far the most important conjugation pathway in man. A multigene family encodes the precise UGTs and a relatively small number of the human UGT enzymes catalyse the glucuronidation of a wide range of the structurally diverse endogenous (bilirubin, steroid hormones and biliary acids) and the exogenous chemicals.

Genetic variations and single nucleotide polymorphisms (SNPs) within the UGT genes are quiet remarkably common, and lead to genetic polymorphisms. Some polymorphic UGTs have demonstrated the significant pharmacological impact in addition to being relevant to the drug-induced ADRs. Two major isoforms of UDP-glucuronosyltransferase, UGT1A1 and the UGT1A9 (Gasic et al., 2018), have been shown to display genetically determined wide interindividual variability in their bioactivities. Studies investigating the role of UGT1A isoforms in the metabolism of drugs such as the irinotecan, flavopiridol, tranilast and the atazanavir have been most valuable in explaining the safety issues (myelosuppression, diarrhoea or the hyperbilirubinaemia) associated with the use of these drugs. A meta-analysis by researchers identified 131 specific drugs, 55drug classes, and 19 therapeutic drug

categories as being allied with ADRs. All except three of these drugs were encompassed among the top 200 selling drugs in the United States.

The therapeutic categories allied with the most common ADRs were cardiovascular, analgesics, psychoactive drugs and antibiotics. This meta-analysis encompassed 18 of 333ADR studies and 22 of 61 variant allele review articles. It identified 28 drugs frequently cited in ADR studies. Among these drugs, 59.2% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 22.2% of randomly selected drugs were metabolised by enzymes displaying genetic polymorphism ($p = 0.006 - < 0.001$). These data suggest that drug therapy based on the genotype of the individual patients may result in a clinically important reduction in adverse outcomes (Xue et al.,2015).

PHARMACOGENETICS AND TRANSPORTERS

For the vast majority of drugs, however, the reason for the individual susceptibility to ADRs has remained unknown and there are hardly any data on the genetic susceptibility (Tissing et al., 2005). However, recent studies have shown that organ-specific organic anion and the cation transporters play an important role in the transport of the drugs into the cells. These transporters may account for drug induced toxicity, hitherto termed ‘‘idiosyncratic’’. The Molecular studies have found evidence of genetic polymorphisms of these transporters in the hepatocytes. Mutations in the genes coding for these transporters may pave to dysfunctional polypeptides, which affect not only the pharmacokinetics of the drugs concerned but also the biopotential hepatotoxic effects of some of these drugs (Eipel et al.,2013).

Furthermore, the variant alleles mainly show inter-ethnic differences that may possibly explain inter-ethnic differences in the hepatotoxic biopotential of a drug (such as ibufenac). Studies investigating these transporters in the patients with hepatotoxicity offer exciting prospects for exploring the potential role of the pharmacogenetics in drug-induced hepatotoxicity. These transporters and the P-glycoproteins co-localise in organs of importance to drug disposition (the intestine, liver and kidney). The expression of the P-glycoprotein activity is under the control of the MDR1 gene and is an important factor in the disposition of many drugs. In the multi-drug resistance (MDR), the processes involved show the considerable interindividual and inter-ethnic variability. For example, a variant allele

recently designated as MDR1*2 (resulting from three linked SNPs) occurred in 62% of the European Americans and only 13% of African Americans. The MDR1 gene and its variants have significant implications in the terms of efficacy or development of the resistance to anticonvulsants, antineoplastic therapy and anti-HIV drugs (Lin et al.,2016).

LONG TERM BENEFITS

An anticipated product of the pharmacogenomics is a more effective health care system. By precisely integrating a patient's clinical history with genetic predispositions, a physician would be more likely to garner accurate recommendations. With confidence in the health care system, a patient's behaviour toward health may improve. Because of the high number of the ineffective prescriptions today, one-half of all patients discontinue their medications for treatment of the chronic conditions after one year. Implications of genetic testing The first type of genetic test would identify individual's drug uptake – from the absorption, to distribution, to metabolism, to excretion. The second type of test would focus on the matching individuals to certain drug compounds to in//crease effectiveness. Finally, the genetic testing would identify those individuals with higher risk for certain conditions (Inaba et al., 2010).

CONCLUSION

A pharmacogenomics database, which is curated which primarily list all the drug discoveries fur specific genetic mutation. The Glucuronidation process by UDP-glucuronosyltransferases Conjugation reactions such as Glucuronidation mediated by the UDP-glucuronosyltransferases (UGTs) are now also attracting increasing attention, especially in the stream of oncology. The impact of influence of the CETP (cholesteryl ester transfer protein) on patients HDL levels. In another case, a person having the deactivating mutations due to the Januskinase 3, their process are vividly reviewed.

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