

PHARMACOGENOMICS -A GENOME BASED DRUG TAILORING

Abstract

Pharmacogenomics is an essential part of clinical genomics that have an effect on increasing number of patients and is used to provide precision medication. Unfortunately, as a result of this genetic variety, there is a lot of variation in drug response across people, which means that no prescription is safe and effective for everyone. A fundamental and unresolved issue in modern medicine is the debilitating and often fatal effects of adverse drug reactions (ADRs). Pharmacogenomic approaches attempt to refine the aim of personalized medicine by utilizing an individual's germline and somatic DNA signatures to guide treatment. It has the potential to revolutionize the practice of medicine by individualization of treatment through the use of novel diagnostic tools. Single Nucleotide Polymorphisms (SNPs) hold the key to defining the risk of an individual's susceptibility to various illnesses and response to drugs. This article includes the clinical implementation of pharmacogenomics in clinical practice, genes involved in the metabolism of the drug, and the application of pharmacogenomics in various disease.

Keywords: Pharmacogenomics
Pharmacogenetics, SNP (Single Nucleotide Polymorphs) & Application of pharmacogenomics.

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I. INTRODUCTION

The idea of pharmacogenomics was first framed by an American geneticist Arno Moltulskey over five decades ago during those time it already became clear they could be variation in drug response due to the effects of genetic inheritance. Succeeding some reports described the contribution of genetics to variation in drug effects [1]. Pharmacogenomics is a challenging and emerging field of therapy, there are several factors such as environmental factor, weight, age, gender and metabolism which affects the drug's efficacy there are many genetic variants in which some variants are associated with drug response and some variants are associated with risk of developing disease [2]. In population-based studies, the pharmacogenomic concept was evoked by defining genomic loci or genes which are corresponded with the difference in drug response in a group of unrelated individuals. Pharmacogenomics assures the promotion of precision medicine and personalized therapy. Pharmacogenomics brings up a method of prescribing medication by the use of genomic information rather than standard medication for all populations [3]. This brings a lower risk for adverse reactions and is effective in treating the individuals. There are more than 125 drugs approved by FDA which has pharmacogenomics information on their label and are boxed with warnings. These drugs are prescribed only after acquiring the genomic data and the drugs are prescribed to the patient [4]. CPIC organization formed by an NIH-funded pharmacogenomic research network and evidence-based guidelines series are promoted on gene-gene interactions which enables the translation of clinical test results into prescribing decisions for specific drugs [5]. If any variation in the dose variation can lead to serious life-threatening adverse drug reactions, so all the pharmacogenomic information is collected EHRs and this information is the major component of the therapeutic encounter [3]. Pharmacogenomic approaches reduce the therapeutic cost for patients since all these drugs are prescribed based on the weight, lifestyle, age, sex, and function of the liver and kidney [6]. This article is based on pharmacogenomics in the future application and scope of pharmacogenomics in recent times.

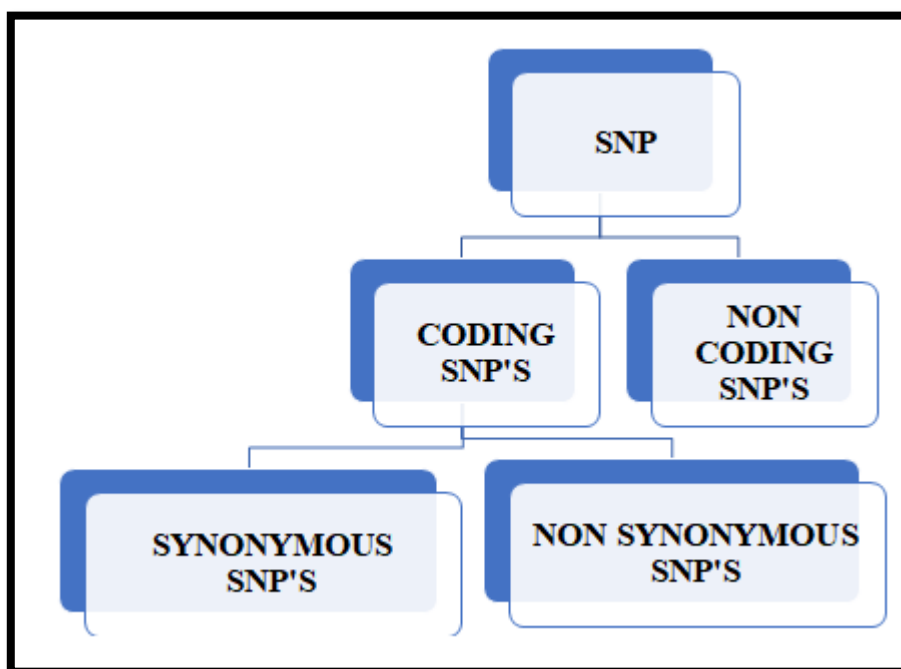
II. PHARMACOGENETICS AND PHARMACOGENOMICS

The term pharmacogenetics is often interchangeably used in the case of pharmacogenomics. Pharmacogenetics is defined as a study of variation in the drug response due to hereditary factors. The addition of the suffix “omics” has introduced the term pharmacogenomics [7].

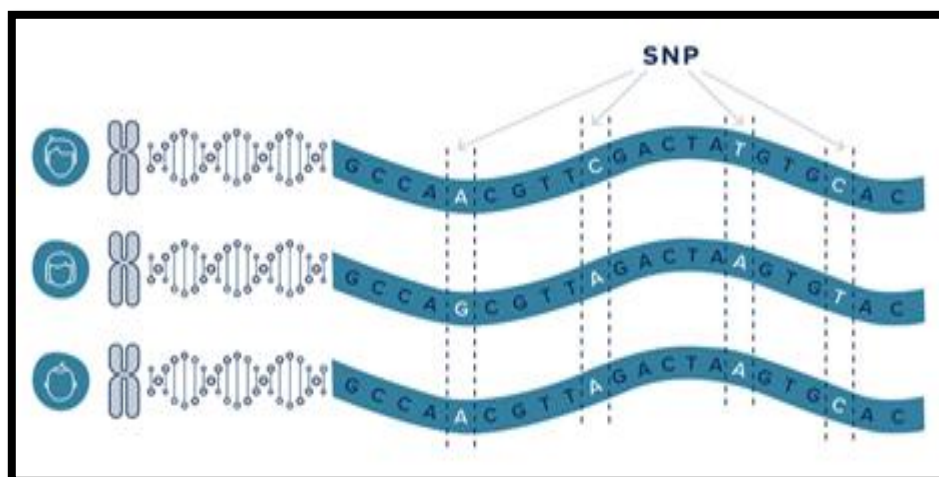
Pharmacogenomics is one of the most interesting fields in the post-genomic era which is broadly defined as the study of the impact of the genetic variation in toxicology and the efficacy of the drug [8] Pharmacogenomic has wide application in clinical genomics the evolution of pharmacogenomics begins with the encoding genes which are involved in the metabolism of the drug. The variation in the drug response is due to single nucleotide polymorphism and genes [9]. The pharmacogenetics – pharmacogenomics effects are those that influence the concentration of the drug reaching its target site called as pharmacokinetics factor those which involve in the target site called as the pharmacodynamic factor on administering a drug to the patient the drug substance is absorbed and distributed to its site of action where the interaction with its target takes place in the case of pharmacogenetic drugs it acts on the specific site and brings genetic variation in the drug target or the signaling cascades downstream from the target site latter cases involve a pharmacodynamic factor[10].

III. SINGLE NUCLEOTIDE POLYMORPHISM

SNPs play a crucial role in the VDR due to its chromosomal variety. Adenine, guanine, thymine, and cytosine are DNA bases. Whereas adenine and guanine are purines, cytosine and thymine are pyrimidines. In which adenine pairs with thymine and guanine bonds with cytosine in some cases scientists observed "mispairing" in which a guanine base theoretically 1% of the total population exists with base mispairing this mispairing is considered a single nucleotide polymorphism this mispairing is considered a single nucleotide polymorphism [11].



SNP is available in both coding and non-coding forms. In which the coding SNP's are classified into synonymous SNP'S and non-synonymous SNP's. synonymous SNPs don't affect the protein sequence and non-synonymous SNPs change the amino-acid sequence [17]. In the year of 2000 complete sequencing map of human genome sequence variation containing 1.42 million have been identified by International SNP map working group[12].



IV. APPLICATION OF PHARMACOGENOMICS IN THE MEDICINAL FIELD: PARKINSONS DISEASES [PD]:

Parkinson's disease is a neurodegenerative disorder that is associated with different pathogenic risk factors like genetic defects, free radicals, focal cerebrovascular damage, drugs, toxins, and pesticides [13]. The neuropathology of PD is characterized by the loss of dopaminergic neurons in the substantia nigra. It is also due to the deposition of Lewy bodies in the midbrain [14]. The neuropathological phenotype of the PD includes the following: epigenetic factor, genomic factor, oxidative stress abnormalities, neuroimmune reactions, dysfunction of the ubiquitin-proteasome system, and metabolic deficiencies all these mentioned above account for the misfolding of proteins, aggregation of Lewy bodies, and dopaminergic neuronal death [15]. Autosomal recessive and dominant forms of PD are caused due to a series of mutations in the primary genes. Mutations in some gene - eg. Microtubule-associated protein tau (MAPT), Parkin 2 (PARK2), PTEN-induced putative kinase 1 (PINK1), PARK7, α -Synuclein (SNCA), Bone marrow stromal cell antigen 1 (BST1), Leucine-rich repeat kinase 2 (LRRK2) these mutation causes familial forms of PD [16]. on performing genome-wide association studies performed showed with over 7 million variants, 26 loci have shown the significant association with PD. And this GWAS also confirmed that 24 single nucleotide polymorphism and conditionally analyzed within four loci —Diacylglycerol kinase θ , Human leukocyte antigen (HLA), 110kD (GAK-DGKQ); SNCA; β -Glucocerebrosidase (GBA); with a second independent risk variant [17].

V. PHARMACOGENOMIC EFFECTS OF ANTIPARKINSONIAN DRUGS

Pharmacogenomic accounts for 60% to 90% of the pharmacodynamic and pharmacokinetic properties of the antiparkinsonian drugs. The genes which are involved in the pharmacogenomic network include metabolic, transporter, pleiotropic, mechanistic, and pathogenic genes and these genes are also influenced by epigenetic modifications which include mRNA regulation, and chromatin remodelling, and DNA methylation.[18]

VI. GENES RESPONSIBLE FOR L-DOPA AN ANTI- PARKINSONIAN DRUG

Table 1: [18]Proton Pump Inhibitors

Pathogenic Gene	ANKK1, BDNF, PARK2, and LRRK2
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Mechanistic Gene	e CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, and OPRM1
Mebolising Genes	e COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP2B6, CYP3A4, CYP3A5, DBH, DDC, G6PD, MAOB, TH, UGT1A1, and UGT1A9
Transporter Gene	Solute carrier family 6 member 3 (SLC6A3)
Pleiotropic Gene	ACE, APOE, and ACHE

Acid-related disorders are treated by proton pump inhibitors these are used to treat a wide range of gastroesophageal disorders which include peptic ulcer disease, erosive esophagitis, and gastroesophageal reflux disease (GERD), eosinophilic esophagitis and Helicobacter pylori (H. pylori) infection [19]. The drugs which are used as the first-generation PPI include lansoprazole, pantoprazole, and omeprazole. The second-generation PPIs include dexlansoprazole, esomeprazole and rabeprazole. Comparing the first-generation PPI with second-generation PPI, second generation PPI's achieves rapid action and inhibition of acid secretion. PPIs are basic in nature they are absorbed in the small intestine and they reach the parietal cells via systemic circulation. PPIs get activated in an acidic environment due to their alkaline nature [22]. Drug substance undergoes irreversible binding with the H⁺/K⁺-ATPase proton pump and this action inhibits the secretion of acid [21]

VII. METABOLISM OF PPI's

The metabolism of PPIs takes place in the liver by the action enzymes like CYP450 and CYP2C19 enzyme, to a lesser extent, it is metabolized by the CYP3A4 [20]

Activity	Metabolizing Enzyme
Ultra-Rapid Metabolizer	CYP2C19*17 / CYP2C19*17
Rapid Metabolizer	CYP2C19*1/ CYP2C19*17
Normal Metabolizer	CYP2C19*1/ CYP2C19*1
Intermediate Metabolizer	CYP2C19*1/ CYP2C19*2, CYP2C19*1/ CYP2C19*3
Poor Metabolizer	CYP2C19*2/ CYP2C19*2, CYP2C19*3/ CYP2C19*3, CYP2C19*2/ CYP2C19*3

Table 2: ²⁰

The ultra-rapid metabolizing takes place by the two sets of CYP2C19*17 and this enhances the clearance of CYP2C19. On the copy of CYP2C19*17 and CYP2C19*1 rapidly metabolizes the drug. Normal metabolizer carries two copies of the CYP2C19*1 allele [20]

VIII. RHEUMATOID ARTHRITIS

RA is an autoimmune disease with a universality of 0.5-1% in the population of human's characteristics are cartilage damage, hyperplastic synovium and bone erosion. Here the proliferation of fibroblast-like synoviocytes (FLS) and the dysfunction lead to

hyperplastic synovium. The cells produce proteinases (eg: matrix metalloproteinases) and cytokines which results in the accumulation of immune cells in synovial fluid [23]. Methotrexate (MTX) – an antifolate agent is a disease-modifying anti-rheumatic drug (DMARD) preferred for RA treatment. A sequence of amino acid is a shared epitope (SE) at positions 70-74 in the HLA-DRB gene. Combination DMARD therapy is slightly higher in results whereas MTX monotherapy shows fewer results in SE-positive patients. Transporting the MTX across the cell membrane is done by the SLC gene which has been studied. MTX uptake is enabled by RFC protein, encoded by the SLC19A1 gene. An increase in intracellular MTX level gets involved in the genetic variation of SLC19A1. ATP-binding cassette proteins transport the MTX present in the cells. The MTX transport pathway is associated with ABCB1C3435T polymorphism seems that the MTX efficacy is implicated by the polymorphism [24]. The association of the single strongest genetic sequence of RA is constituted by the HLA-DRB1 alleles, which contribute nearly 30% of the total genetic component of the disease. [26]

Uptake of DNA methylation is due to the MTX biomarker, this results in the addition of methyl group to cytosine-guanine(C-G) dinucleotide (CpG). CpGs are methylated for nearly 70-80% across the genome and CpG islands are the cluster form of the gene promoting regions, it is a transcriptionally active gene when hypomethylated. For example, EWAS compared the 354 RA cases with its DNA methylation at 485000 CpG and 10 different methylated CpG sites along with the MHC region and in 337 healthy controls and which is known as RA genetic risk loci[25].

IX. GENES INVOLVED IN PHARMACOGENOMIC ACTION RHEUMATOID ARTHRITIS

Transporte Gene	RFA1C1-SLC19A1, RFC1G80A, PCFT-SLC46A1
Export Gene	ABCC5, ABCC4, ABCC3, ABCC2, ABCC1, &ABCG2

Table 3: [23] **Type 2 Diabetes**

Insulin aversion and continuous decrease in insulin secretion out-turn to the chronic metabolic disease type 2 diabetes, consequence in hyperinsulinemia, impaired glucose utilization dyslipidemia and dysfunction of the pancreatic beta cell. The response of therapy to the genetic variations which are shown in the drugs mainly used for T2D treatment is DPP-4 inhibitors/ GLP1R agonists, biguanides (metformin) and sulfonylureas/ meglitinides. Drug-gene interaction would allow translating of the gene into clinical practice-which helps in decision making on therapy, reducing the side effects, and differentiating and segregating the patient group [27]. OCT3, OCT2, MATE2 and MATE1 are the significant transporter proteins which affect the pharmacokinetics of the drug metformin. SLC22A2 and SLC22A3 genes encoded OCT2 and OCT3 [30]. Here, OCT2 is in charge of the production of metformin, that is released in the bloodstream and then excreted out through urine. OCT3 oversee the take up of metformin from the liver and the intestine where the elimination and absorption are interlinked with the mutation that takes place. SLC47A1 and SLC47A2 genes are encoded MATE2 and MATE1. MATE1 is responsible for the efflux transportation with metformin, and MATE2 is also responsible for the efflux transporter. The response of these transporters takes part in the renal tubular region i.e introduction of metformin into the urine from the renal tubules. KCNJ11, MTNR1B, and MADD gene polymorphisms supervise

insulin release. If a mutation in KCNJ11, the potentiality of ATP is decreased to inhibit KATP channels and improve the MgATP channel's action leading to the reduction in the release of insulin [28].

1. **Metformin:** GLUT2 transport is decreased, and the comeback result is good. Side effects with reduced PMAT expression, OCT1 transport and SERT genotype [29].
2. **TZDs:** CYP2C8 and SLCO1B1 activity alters the weight gain and response along Rosiglitazone [29].
3. **Sulfonylureas:** (CYP2C9) metabolism of SU is delayed which is 3.44 times preferred [29].
4. **DPP4 inhibitors:** If in CTRB1/2 variation occurs leads to a 0.5% difference in HbA1c decrease [29].

X. INVOLVED IN PHARMACOGENOMIC ACTION TYPE 2 DIABETES

Asthma is a persistent respiratory disease that shows inflammatory characteristics in the lower airways which need long-period medication [34]. It is one of the complex syndromes and multiple gene studies help in the clinical development. The phenotype of asthma is characterized by bronchial hyperresponsiveness, respiratory tract infection in the early stage, airway inflammation, allergic sensitization in childhood and a decrease in immune system maturation [31]. The pharmacogenomic development has provided the pharmacogenetic association with asthma exacerbation and despite the use of common treatments: ICS, LABA, SABA, and LTRA. Both SABA and LABA increase the airflow by the activation effect on beta2 adrenoceptor in bronchial smooth muscle. The ADRB2 encoding gene is usually used in pharmacogenetics in asthma [32].

Transporter Gene	SLC22A2(OCT2), SLC22A1(OCT1), SLC47A2(MATE2), SLC47A1(MATE1) [27]
Insulin Secretion Gene	KCNJ11(rs4148609), HNF4A(rs1108692), ABCC8(rs4148609), HNF1B(rs11868513) [29]
Insulin Sensitivity Gene	CAPN10(rs758027), ADIPOR2(rs758027), GCK (rs2908289) [29]
Metabolising Gene	MEF2D(rs6666307), MEF2A(rs4424892) [30]

Table 4: Asthma

1. **Beta 2 agonist response (SABA):** e.g. Albuterol, terbutaline, and salbutamol are the usually recommended prescription. These are mainly used for the relief basis "as needed" to lessen bronchoconstriction by dilating the bronchi. The candidate gene studies centred on encoding the gene of beta2 adrenoceptor-ADRB2 by which the drug binds to the cell membrane. There are two different genetic variants which are associated with SABA. One of the variants-Gy16Arg (frequency of allele ~40%) of the protein receptor at position 16, glycine acts as a substitute for the arginine and the other variant-Gln27Glu (allele frequency~45%) at the position 27 glutamic acid converted into glutamine. These changes in the variants impact the down-regulation of the receptor in the In vitro studies [33].

2. Long-acting beta-2 agonists (LABA): e.g. Formoterol and salmeterol, also act on the beta2 adrenoreceptor, but long action (8-12 hrs vs 3-5 hrs for SABA). LABA pharmacogenetic responses and studies were mainly performed on the ADRB2 gene. Whereas in adults, no effects showed on retrospective studies on the ADRB2 genotype for the enhancement of lung function. The Arg16 variant's effect is determined by the LABA in patients with moderate asthma but not any chance of exacerbation and very poor lung function [34].

XI. GENES INVOLVED IN PHARMACOGENOMIC ACTION IN ASTHMA

Table 5

Saba Gene	Adrb2(Rs1042713) [32]
Laba Gene	Adrb2(Rs1800888), Adbr2(Rs1042713), P2rx7(Rs2230911) [32]
Transporter Gene	Mrp7/Abcc7, Slc02b [33]
Ltm Pharmacokinetic Gene	Cpy2c9, Cyp3a4 [33]
Ltm Pharmacological Leukotriene Pathway Gene	Alox5, Lta4h, Cysltr7&Ltc4s [33]

XII. CONCLUSION

Barriers remain to the implementation of pharmacogenomic-based precision medicine, but many advances have been made in the past decade. It is now clear that pharmacogenomics, as a clinical discipline, is being applied at the bedside to enhance the care of patients who are suffering from a variety of diseases and are being treated with a variety of drugs. The challenges will then be to demonstrate convincing links between genetic variation and drug responses and to translate that information into useful pharmacogenomic tests, pharmacogenomics has paved the way in the development of personalized medicine which avoids adverse drug action by optimizing drug dosage and ultimately this provides patients to select the right drug at the right dose for the right patient.

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