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Pharmacogenomics and Diabetes: Current Progress and Prospects

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Abstract. Pharmacogenomics describe the influence of an individual's genes on the drug response. With the wide variety of genetic diversity in individuals the response to drugs is also varied. The genetic makeup of a person influences the drug metabolism as well as its efficacy and the appearance of adverse drug reaction. By studying this relationship between the genes and the drugs can formulate an individualized treatment which is specific to a person in terms of dosage and efficacy. This would lead to an overall improvement in drug therapy by improving the safety, efficacy profile and reduce the cost and time of treatment and occurrence of adverse side effects. Pharmacogenomics is important in the development of new drugs. High rate of response variability exist among diabetic patients as a consequence of genetic diversity of the genes involves in drug response and transport. This review will summarize the targeted strategies towards the genetic variation studies based on drug response and the drug response towards candidate gene involved in diabetes. With the use of pharmacogenomics tools, clinical and genetic data from the patients, it is possible to formulate treatment plans that can reap remarkably favourable results.

Keywords: drug targeting, SNPs, drug development, diabetics, genome, nucleotide polymorphisms

Introduction

Role of pharmacogenomics in drug development. Pharmacogenomics is a rapidly emerging field of medical science. It is a vast subject where large-scale studies are being done for the purpose of research on the effect of gene mutations on drug response (Surendiran *et al*., 2008). Many of the drug compounds fail to emerge as an effective therapeutic agent by the end of the clinical trials. This can be as a result of the trial drugs' inefficacy or adverse effects. Studies suggest that the drugs with targets identified by human genomic studies have better chances of being successful by the end of the clinical trials (Roden *et al*., 2019). Clinical trial pharmacogenomics use is still a relatively novel idea. Before the advent of pharmacogenomics, there was low predictability in terms of efficacy and safety of the drug under trial. Majority of the drugs failed to reach therapeutically useful stage before the trials ended which led to heavy loss of time and money as summarized in Fig. 1. However, the situation has changed as a result of the application of sophisticated pharmacogenomics technologies, there is better patient selection, dose selection and dose modification that increases the predictability of efficacy and safety of the drug which in turn leads to decrease of financial resource loss as well as time. Furthermore, the results of the trials as well as the interpretation of the reported adverse reactions become more accurate with the help of pharmacogenetic testing data (Surendiran *et al*., 2008).

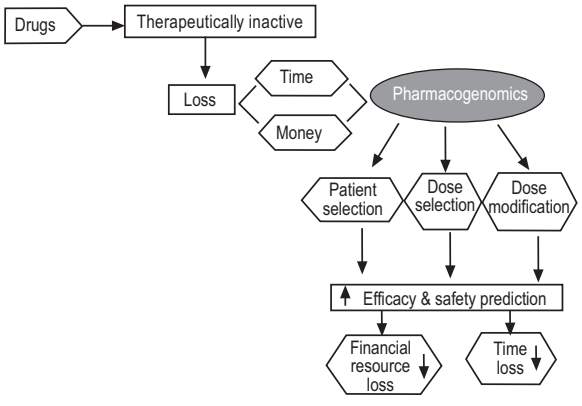

Fig. 1. The Potential role of pharmacogenomics towards drug development.

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The efficacy of any drug under trial to a great extent depends upon the target group. If the target group is effectively determined before starting the trial, there are better chances of success of the trial. Through pharmacogenomics integration in delivering of new medicines for drug discovery and development process drugs developed with the help of pharmacogenomic methods have an edge as the target is identified prior to the beginning of the trial and hence has a pre-determined efficacy. For example, during the trial for drug trastuzumab for metastatic breast cancer, it was found during initial phases of the trial that the said drug was effective only in those females that showed over expression of the protein HER_2. Therefore, the following phases of the trials excluded those women who did not show over expression of HER_2 protein and later on the drug was approved. This example clearly demonstrates that when the target is stratified genetically, the efficacy of a drug is better expressed (Surendiran *et al*., 2008).

Another important aspect of pharmacogenomics that enhances the process of new drug development is the identification of rare gene variants that are linked to specific human phenotype. For example, $PCSK_9$ in which the gain of function variant leads to increase in the LDL-cholesterol and familial hyper-cholesterolemia. However, there is a rare gain of function variant that leads to the completely opposite effect. It is associated with significant decrease in LDL cholesterol. This prompted the development of $PCSK_9$ Inhibitor drugs for the treatment of elevated LDL and hyper-cholesterolemia. Similarly, there are many other rare variants that provide basis for the development of specific drugs (Roden *et al*., 2019). Through medicinal chemistry field now it's possible to identify, design, develop and synthesize drugs with a therapeutic potential with comparative analysis of existing available drugs as shown in Fig. 2.

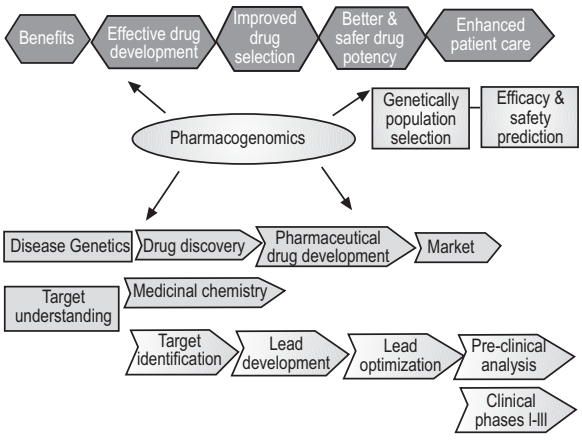

Fig. 2. A road map of pharmacogenomics from drug discovery to pharmaceutical development process used for treatment and therapy.

Methods of studying genetic variation affecting drug response. ***Candidate gene approach.*** The candidate gene approach involves establishing a link between different allelic variants or SNPs (single nucleotide polymorphisms) within the candidate gene and drug response variability in order to identify genetic determinants of drug response variability (Surendiran *et al*., 2008). The selection of a suitable candidate gene that may plausibly play a role in the process or disease under investigation is the initial and crucial step in carrying out candidate gene investigations (Cunningham and Chapman, 2019). Genes encoding for the drug metabolizing enzyme, drug transport proteins, cellular pathways proteins and receptor proteins, among others, may be candidate genes for a drug response. Allelic variants in the candidate gene are investigated. A candidate gene may contain several allelic variations or SNPs (Surendiran *et al*., 2008). Following selection of the candidate gene, polymorphism has to be decided in association to the study. It is necessary to first categorize the various gene variants that already exist before determining which of those variants lead to proteins with altered activities that may have an impact on the target trait of interest. This method makes use of case and control, involving members from the affected family or unrelated members (Kwon and Goate, 2000). Candidate gene studies have the drawback of producing misleading relationships if the case and control groups are not well matched (Surendiran *et al*., 2008).

An example of this method is studying alcoholism in humans. Genes encoding enzymes involved in different processes of alcohol metabolism, such as aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH) are rational options when studying alcoholism. in which both enzymes are encoded by numerous genes and that each of these genes has a large number of alleles, candidate gene analysis is possible. According to studies the enzyme encoded by an ALDH allele

termed ALDH2*2 degrades acetaldehyde more slowly than usual, prolonging unpleasant alcohol symptoms like nausea, facial flushing and heart palpitations. Carriers of the ALDH2*2 allele drink less alcohol and are less likely to develop alcoholism than those without it. This is because it tends to have a protective impact against alcoholism. This allele is particularly prevalent in various Asian groups (Kwon and Goate, 2000).

Genome-wide association studies (GWAS). Genome wide scan is an extensive method of studying the effect of genes on drug response. This strategy involves compiling an SNP map from the entire set of allelic variants found in the human genome. This is investigated to see if the gene has anything to do with drug response variability (Surendiran *et al*., 2008).The purpose of genome-wide association studies (GWAS) is to find single nucleotide polymorphisms whose allele frequencies change consistently as phenotypic trait values change (Marees *et al*., 2018). GWASs use a case control design, where SNP frequency and distribution is compared between individuals with disease or trait (cases) and those without disease or trait (controls) (Perera and Minoli, 2021). Once the samples are taken from case and control, the machines rapidly scan each participant's genome for single nucleotide polymorphisms, or SNPs, which are strategically, placed markers of genetic variation. When some genetic variants are found to be substantially more common in people with the disease than in people without the disease, the variations are said to be "related or associated." The associated genetic variants will function as powerful arrows pointing to the part of the human genome where the disease causing issue. The associated variants, on the other hand, may not be directly responsible for the disease. It's possible that they're simply "tagging along" with the real causal variants. As a result, researchers often need to take extra measures, such as sequencing DNA base pairs in that specific region of the genome, to pinpoint the exact genetic change causing the disease (Uffelmann *et al*., 2021).

Haplotype analysis. Haplotype analysis for drug response variation is the study of SNP clusters in linkage dis-equilibrium on a chromosome and their relationship to drug response. In contrast to a genome-wide scan only a subset of haplotypes is examined rather than the entire genome. Selective SNPs are grouped into haplotype blocks and utilizing family studies, their linkage dis-equilibrium is assessed. The haplotype blocks are then examined for connections to clinical outcomes. This method is cost effective and provides more information as compare to single nucleotide polymorphisms (Surendiran *et al*., 2008).

Pharmacogenomics guided treatment of diabetes. Diabetes is a highly prevalent disease affecting a large portion of the world population. Among these, majority of the cases fall under the category of Type 2 diabetes (T2D). It is a complex disease with significant etiological variation and as the cases are on the rise, optimization of the treatment regimen is entirely essential. Since the introduction of GWAS, research on the effects of inherited and acquired genetic differences on pharmaceutical response has progressed from pharmacogenetics to pharmacogenomics, with a move from single candidate genes to GWAS. Even patients on comparable anti-diabetic regimens show significant diversity in drug disposition, glycemic response, acceptability and the occurrence of side events in the clinic (Dawed *et al*., 2023). This inter-individual heterogeneity is caused by certain gene polymorphisms implicated in the transport, metabolism and therapeutic processes of oral anti-diabetic drugs. Pharmacogenomics is on the agenda to determine whether genetic testing may be used to predict treatment outcomes in order to provide type-2 diabetes patients with better care (Gershon *et al*., 2014). Currently the most often used medications for treating type 2 diabetes as shown in Fig. 3. In recent years, extensive pharmacogenetic studies of anti-diabetic medications have been carried out discovering a large number of SNPs impacting both the pharmacokinetics and pharmacodynamics of these medications (Flaten and Monte, 2017).

The pharmacogenomics of a drug's efficacy is categorized as pharmacokinetic and pharmacodynamics variation, as shown in Fig. 4. It is useful to categorize pharmacodynamic variation into differences in medication response that reflect the underlying etiological variance and differences in the context of a complex disease like type 2 diabetes where there is extensive etiological variability. Since the majority of diabetes treatments aim to correct the pathophysiological defects that lead to the development of diabetes, different etiologies are likely to have an effect on how the body reacts to drugs that target this pathway. As a result, it may be predicted that pharmacogenomics of that condition will help us understand the genetic etiology of diabetes (Gershon *et al*., 2014).

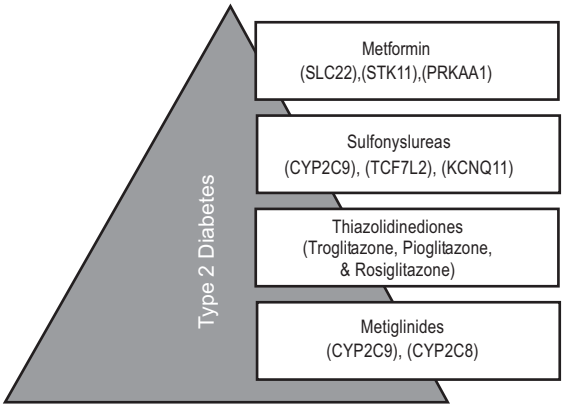

Fig. 3. Gene polymorphisms of diabetes. It could affect how diabetes patients receiving anti-hyperglycemic drug therapy is managed therapeutically.

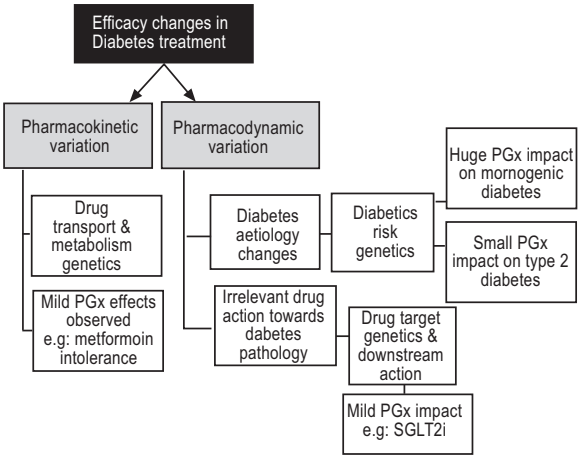

Fig. 4. Evaluating PGx in type 2 diabetes. PGx, pharmacogenetics; SGLT2i, sodium glucose transporter 2 inhibitor.

Metformin pharmacogenomics. Metformin is the first-line medication for the treatment of type 2 diabetes. It has been in therapeutic usage for almost 60 years and it comes from the French lilac. However, its mechanism of action is still up for debate. Metformin is a highly successful medication for losing weight and possible cardio protection and it is being studied for its potential benefits on cancer risk and outcomes. However, it should be noted that 10% of people who get metformin experience serious gastrointestinal (GI) side effects, which result in 5% of persons quitting their medication treatment (Damanhouri *et al*., 2023). The mechanisms of GI intolerance are equally unknown. The significant advantages come with a lot of questions about the mechanism of action and negative effects (Pearson, 2019; Pawlyk *et al*., 2014).

A genome wide association study (GWAS) was carried out in 2 diabetes patients on metformin in an effort to comprehend the metformin mechanism, HbA1c decrease was seen after initiation as the outcome. In this trial, there was a considerable inter-individual variation in metformin response with some patients having a drop in their percent A1C of about 4%, while others showed no change or significant rises in A1C after medication. It was further discovered that the glycemic response to metformin was associated with a locus on chromosome 11 that contains the genes NPAT and ATM (Pawlyk *et al*., 2014). The ataxia telangiectasia mutant gene (ATM), which encodes a serine/threonine kinase, may regulate enzymes implicated in metformin response (Chen *et al*., 2022). Despite the fact that the investigators reported *in vitro* evidence indicating that ATM was involved in metformin's activation of AMPK in cell cultures, it has been shown that the molecule utilized to inhibit ATM in the *in vitro* cellular research is really an OCT1 inhibitor. Because OCT1 is the primary metformin transporter in the liver and hepatic cell lines, the ATM inhibitor inhibited metformin activation of ATM by blocking the drug from entering the cells, making the results much more difficult to interpret. This implicates the necessity of further studies to explore the pharmacogenomics association with metformin response (Pearson, 2019; Pawlyk *et al*., 2014).

In another study, the 9% of white Americans who have two copies of the C allele had a 0.33% lower HbA1c than the ones having two copies of the T allele in obese people. This is the equivalent of a 550 mg change in the dose of metformin. It is anticipated that the homozygous excellent response C allele, which is present in 49% of black Americans, will have a significant impact on the ethnic group's reaction to metformin. Metformin being a cheap and effective drug with multiple benefits is highly unlikely to be replaced as the first line drug even though its efficacy may be low for some patients. Hence, the studies need to be done to help establish genotype based dosing of metformin (Pearson, 2019; Pawlyk *et al*., 2014).

Sulfonylureas (SU) pharmacogenomics. The sulfonylureas stimulate beta-pancreatic cells to secrete insulin. Tolbutamide, tolazamide, chlorpropamide and acetohexamide for examples of first generation sulfonylureas. Glyburide (also known as glibenclamide), glipizide, gliclazide and glimepiride are second generation sulfonylureas (Aquilante, 2010). The sulfonylurea receptor 1 (SUR1), which is the regulatory subunit and the inward rectifier potassium ion channel (Kir6.2), which forms the channel's pore, make up the KATP channel complex. The KATP channel is made up of four SUR1 subunits and four Kir6.2 subunits (Reis and Velho, 2002). Sulfonylureas bind to the KATP channel's SUR moieties, causing channel closure, membrane depolarization and calcium influx *via* voltagegated calcium channels, which results in insulin secretion as shown in Fig. 5. (Pearson, 2019).

The onset of newborn diabetes mellitus is linked to nucleotide changes in genes encoding KATP channel proteins such as ATP-binding cassette, subfamily C, member 8 (ABCC8) and potassium channel inwardly rectifying subfamily J member 11 (KCNJ11). Research on SUs demonstrated that these medicines may be effective in treating T2D patients based on the defects caused by KCNJ11 and ABCC8 mutations (Rafiq *et al*., 2008; Pearson *et al*., 2006). GWAs have demonstrated a substantial link between the KCNJ11 polymorphism rs5219 and T2D (Sun *et al*., 2014). The effects of the

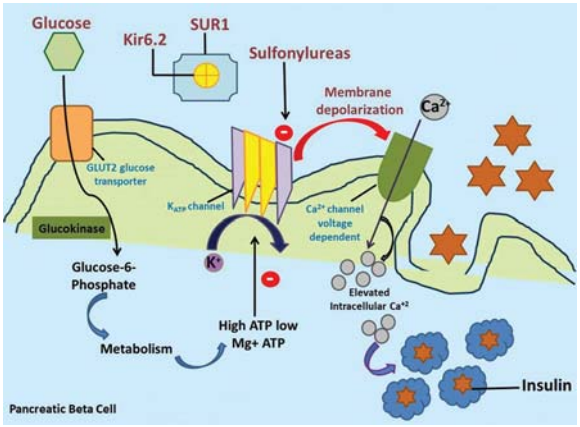

Fig. 5. Mechanism of action of sulfonylurea. The sulfonylurea receptors bind to beta-cell KATP channel complexes that results in cell membrane depolarization leads to series of cellular events for insulin secretion.

K23E amino acid substitution on the therapeutic advantages of SU were found in a population of 101 Caucasian patients (Marees *et al*., 2018). According to the study, "K-allele" homozygous carriers experienced a greater decrease in HbA1c levels after 6 months of treatment than "EE" carriers (Javorsky *et al*., 2012).

TCF7L2 gene nucleotide variants have been linked to the start of T2D as well as the efficacy of SU therapies. TCF7L2 is required for cell survival and glucose-stimulated insulin secretion (GSIS) (Shu *et al*., 2008). Variations in the amount of active TCF7L2 in cells may play a role in determining a gradual deficiency in insulin production and in accelerating T2D progression (Shu *et al*., 2008). A connection between the changes in the CYP2C9 gene and the treatment response to sulphonyl urea has been revealed for the first time by the GoDARTS (genetics of diabetes audit and research, Tayside and Scotland). The cytochrome P450 isoenzyme-2C9 which is encoded by the CYP2C9 gene metabolizes sulphonylureas in liver. As a result, it is evident that some CYP2C9 allelic variations are related to altered pharmacological responsiveness to SUs and/or T2D vulnerability. The major risk alleles for this gene that have been identified so far are CYP2C9 and CYP2C9 (Kirchheiner *et al*., 2002a&b).

Additionally, the Arg (972) IRS-1 variant is linked to an increased risk of secondary sulfonylurea failure and it's worth noting that the genotype frequency of this variant is twice as high in patients with secondary sulfonylurea failure compared to diabetic patients with well controlled blood glucose levels on oral therapy. Glibenclamide is less successful at lowering glucose levels in diabetic people who have risk alleles in the NOS1AP gene (Sun *et al*., 2014). The effects of third-generation SUs medication (in conjunction with metformin) in patients with CYP2C9, KCNJ11 and ABCC8 gene polymorphisms have also been studied in several studies. Finally, recent advances in the realm of sulfonylurea pharmacogenomics have yielded some remarkable results. More detailed studies of these current sulfonylurea pharmacogenomic connections will be required in the future years to evaluate whether genetic information has clinical use in enhancing type 2 diabetes pharmacotherapeutic therapy.

Thiazolidinediones pharmacogenomics. Glitazones are thiazolidinediones that act as agonists for the peroxisome proliferator-activated receptor (PPAR-),

heir molecular target. Direct antioxidant action of glitazones can play a role in their ability to reduce insulin resistance. PGC-1, resist in, adiponectin, leptin, TNF-alpha and CYP2C8 have all been implicated in the pharmacogenetics of thiazolidinediones in recent investigations (Sun *et al*., 2014). It's vital to remember that genetic variation is simply one factor to examine when predicting a diabetic drug's efficacy. In the past, when analyzing drug response, clinical studies did not take patient phenotype into account. Recent research, re-examined these trials and found that even seemingly insignificant factors such as BMI and sex play a role. Thiazolidinediones for example, work well for obese women, while sulfonyl urea work well for slender males. Diabetes patients have been divided into five categories or subtypes based on a more thorough review of phenotype that includes markers of insulin resistance and beta cell activity. These groups are likely to react to diabetes therapy differently. In order to guide treatment decisions, genetic variation will need to be overlaid on top of such clinical and physiological variance (Pearson, 2019).

Pharmacogenomics guided treatment of hypertension. Hypertension is one of the most prevalent and dangerous medical illnesses in the world that is major cause of morbidity and mortality because of its association with various cardiovascular diseases. Despite the fact that there are many medications available, blood pressure control rates are lesser than expected and inter-individual variability of blood pressure response to various treatments is significant (Ansari *et al*., 2023), while certain demographic criteria such as age and sex may influence which antihypertensive drug to choose over another, the variability in drug response can be partially attributed to genetics (Cunningham and Chapman, 2019; Oliveira-Paul *et al*., 2019).

Genetic factors have a large influence on blood pressure changes. So, naturally there are numerous studies that have been conducted over the past years have sought to identify the genes responsible for causing hypertension. These investigations discovered many genetic variants, including insertions/deletions, micro-satellites and single nucleotide polymorphisms to be related with hypertension. Additionally, these studies have demonstrated that genetic variables also have a role in the significant inter-individual variation in responsive to antihypertensive medicine, providing a window for pharmacogenomics research and possibly individualized drug therapy. Thus, the role of pharmacogenomics in hypertension is to choose the best antihypertensive medicine and the most suitable dose using genetic information along with other relevant clinical or demographic characteristics in order to maximize therapeutic efficacy and minimize the risk of side effects (Oliveira-Paula *et al*., 2019).

Calcium channel blockers pharmacogenomics. Calcium channel blockers (CCB) act by blocking the calcium channels found on smooth muscle cells of the heart and blood vessels. They inhibit a calcium ion from entering vascular smooth muscle which relax the muscle and dilate the blood vessels, reduces vascular resistance and as a result, lower arterial blood pressure. Each calcium channel blocker subtype binds to a particular site and the mechanism of action is depicted in Fig. 6 (Rysz *et al*., 2020). Calcium channel blockers are widely used around the world as first line of treatment for hypertension in adults (Türkmen *et al*., 2022).

Various researches have depicted those gene polymorphisms in different ion channels influence the effect pharmacological effect of calcium channel blockers. Some of these channels are large-conductance calcium and voltage-dependent potassium channel 1 (KCNMB1), ERG potassium channel (KCNH2) and voltage-gated calcium channel 1C (CACNA1C), 1D (CACNA1D) and 2 (CACNB2) (Rysz *et al*., 2020). Cytochrome P450 3A5that is present in the liver is responsible for processing calcium channel blockers. Studies suggest

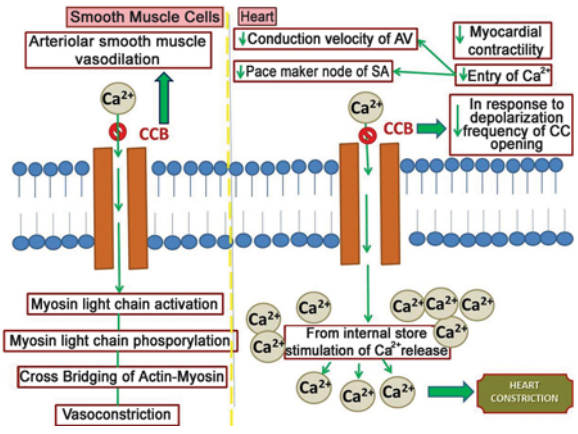

Fig. 6. Mechanism of action of calcium channel blockers.

that variations in the gene that codes for this enzyme maybe responsible for altered responses to calcium channel blockers. Unlike the functioning CYP3A5*1 allele, the CYP3A5*3 variation has a 6986A>G mutation in intron 3, which causes a splicing error and a non-functional protein. A second mutation (14690G>A) in the CYP3A5*6 gene leads in the deletion of exon 7, a splicing error and a protein truncation. Despite CYP3A5's involvement in the breakdown of calcium channel blockers, it is unclear how these CYP3A5 polymorphisms affect CCB reactions. The CYP3A5*3 genotype seen in Chinese people was connected to stronger antihypertensive responses to CCB amlodipine. However, neither Koreans nor African-Americans showed any co-rrelations between CYP3A5 polymorphisms and CCB effects. These variations could be explained by how genetics, environment, and their relationship with ethnicity can influence amlodipine responses (Rysz *et al*., 2020; Oliveira-Paula *et al*., 2019).

Various GWAS have shown the association of SNPs with changes in blood pressure in response to CCB. In this study, found the allele C for rs588076 of the PICALM gene, allele G for rs2429427 of the TANC2 gene, allele C for rs10898815of the NUMA1 gene and allele C for rs564991 of the APCDD1 gene are associated with changes in blood pressure in response to CCB in hypertensive patients in Japan. Another study showed the association of SNP rs12946454 of PLCD3 with response to diltiazem (Pawlyk *et al*., 2014). Although significant research has been done, there is still a need for further elaborate studies in order to reinforce the importance of pharmacogenomics in antihypertensive drug therapy.

Angiotensin-II receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACEi) pharmacogenomics. The control of blood pressure by the renin-angiotensin system is well established. These effects are co-ordinated through inter-dependent mechanisms in the renal, cardiovascular and nervous systems. Angiotensinogen is converted into angiotensin I, which is converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II generates the physiologic effects of the renin-angiotensin system. It controls blood pressure by stimulating the angiotensin II type 1 receptor (AT1R) receptors present in the vascular, renal and nervous systems. This leads to vasoconstriction, reabsorption of sodium and increased sympathetic tone (Rysz *et al*., 2020; Oliveira-Paula *et al*., 2019).

The variation in genes that encode for the components of renin-angiotensin-aldosterone system may affect the pharmacogenomics of angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors. Numerous studies have demonstrated the importance of NOS_3 (nitric oxide synthetase) in pharmacogenomics for ACEi, ARB responses and the heterozygous cells, endothelial cells homozygous for the C allele can respond to ARB olmesartan therapy with significantly elevated NO production. They concluded that hypertension in individuals with the C allele may respond to enalapril and olmesartan more favorably. Another study showed that the NOS3 665C/T SNP (rs3918226) T allele react better to enalapril, as compared to the A allele for the NOS3 tagSNP rs3918188 and the CAG haplotype involving NOS3 tagSNPs (Rysz *et al*., 2020; Oliveira-Paula *et al*., 2019).

In a GWAS, the GG genotype for the SNP rs10752271 in the CAMK1D gene (encoding calcium/calmodulin dependent protein kinase 1D, involved in aldosterone synthesis) was discovered to be related with improved results in response to losartan. Another GWAS showed multiple loci impacting the blood pressure response to candesartan, an angiotensin receptor blocker. The relationships were found with the SNPs rs11020821 in the FUT4 gene, rs3758785 in the GPR83 gene and rs11649420 in the SCNN1G gene, which codes for the enzyme fucosyltransferase 4. SNP rs3814995 in NPHS1 gene was found to be associated with improved blood pressure responses to losartan in another study (Oliveira-Paula *et al*., 2019; Rysz *et al*., 2020). Further studies addressing the efficacy and safety of ACEIs and ARBs are required because they are the most frequently prescribed antihypertensive medicines. In order to identify gene-gene interactions and modifications of effects in genes with many variations, these associations must be investigated in large datasets (Flaten and Monte, 2017).

ß-Adrenergic antagonists (ß-blockers) pharmacogenomics. ß-Blockers are widely used to treat a variety of cardiovascular ailments (Thomas and Johnson, 2020). They are known to decrease blood pressure, reduce myocardial contraction, pulse rate, and heart output. According to various studies, they have positive effects

on endothelial dysfunction and they also play a role in the endothelium and vasculature related mechanisms of decreasing blood pressure (Rysz *et al*., 2020).

The ADRB1-encoded ß1 adrenergic receptor is the main protein target of all ß blockers. The amino acids that are encoded by this gene can change due to two common and genetic polymorphisms: rs1801252, which results in a replacement of serine by glycine at position 49 of the protein (Ser49Gly) and rs1801253. This leads to replacement of arginine by glycine at position 389 of the protein (Arg389Gly). When these two polymorphisms disrupt intracellular signaling mediated by the ß1 adrenergic receptor, they provide significant evidence for functional impact. In relation to variant alleles the ancestral alleles for these polymorphisms (Ser49 and Arg389) are both linked to enhanced intracellular responses to ß1-adrenergic receptor agonists. Although there is functional relevance, there is no solid evidence that the blood pressure response to ß blockers is affected by Ser49Gly or Arg389Gly polymorphisms (Rysz *et al*., 2020; Oliveira-Paula *et al*., 2019).

Gene polymorphisms can control the pharmacokinetics as well as the pharmaco-dynamics of ß blockers. CYP2D6 is a crucial enzyme in ß blocker metabolism. The pharmaco-genetic working group of the Royal Dutch pharmacists association has published guidelines for prescribing metaprolol medication as a treatment of hypertension based on CYP2D6 genotyping of patients based on concrete proof showing that CYP2D6 genotypes influence blood pressure responses to ß blockers. However, the findings of several other researchers have called into question the prescribing of metaprolol medication as a treatment of hypertension based on their CYP2D6 genotype (Rysz *et al*., 2020; Oliveira-Paula *et al*., 2019).

The peoples with one variant allele for the SNP rs201279313 in the SLC25A31 gene have codes for ADP/ATP translocase 4, respond to ß blockers more favourably than people with two wild-type alleles. Additionally, they discovered that people with the deletion allele of rs11313667, which is found in the intronic region of the LRRC15 gene, respond to ß blockers more strongly than people with two wild-type alleles. These relationships were reinstated in a different PEAR (pharmacogenomic evaluation of antihypertensive responses) study, hence validating these results (Oliveira-Paula *et al*., 2019).

The results of the above mentioned and some other interesting studies done on ßblockers are summarized below in Table 1.

As it is evident, that most of the studies focus on the ADRB1 gene. In particular, the Arg389 homozygous genotype has been linked to improved response to ß blockers in a variety of conditions, including glaucoma, heart failure, and hypertension. Even though not all studies, showed a positive connection, but those that did always pointed in the same direction. Results of studies done on other genes have not been as consistent and require further research. ß blocker pharmacogenomics offers hope for the possible clinical application of genetic data to customize ß blocker medication. The identification of other genes in addition to ADRB1 that also contribute to response variability will be crucial. This will be helpful in explaining the diverse reactions to a ß blocker considerably to be translated into clinical application (Shin and Johnson, 2007).

Current success in pharmcogenomics. Variation in a single gene can lead to a significant change in drug response. The same can be clearly understood with the help of pharmacogenomics. Codeine is an opioid analgesic drug. It is present in an inactive form that is converted into its pharmacologically active form, morphine by the enzyme cytochrome P450 2D6 (CYP2D6). In some rare cases, there have been seen serious adverse effects even after receiving standard prescribed doses. With the help of pharmacogenomics, it is now known that the enzyme CYP2D6 is highly polymorphic with numerous genetic variants that are responsible for the varied drug response in different patients (Lee *et al*., 2014).

Vitamin K epoxide reductase complex 1 (VKORC1) is necessary for the activation of vitamin K in the body. Warfarin is an anti-coagulant that inhibits the activity of this complex and thereby reducing the amount of vitamin K available for the production of coagulation factors. Varied responses have been seen in various patients to warfarin. Since the therapeutic window of warfarin in narrow, even minor variations in the dosage can lead to serious adverse drug reactions. Pharmacogenomics has led to the identification of genetic variants in VKORC1 and cytochrome P450

Table 1. Pharmacogenomics of ß-Blockers (Oliveira-Paula and Pereira, 2019)

Gene	Polymorphism	Study type	Study population	Main findings
ADRB1	rs1801253	Candidate gene	Caucasian (n=29), African American (n=10) and Hispanic (n=1) population	Arg/Arg genotype carrier have better blood pressure responses to metoprolol
ADRB1	rs1801253	Candidate gene	Chinese population (n=86)	Arg/Arg genotype carriers have better blood pressure responses to carvedilol
ADRB1	rs1801253	Candidate gene	Chinese population (n=261)	Gly/Gly genotype carriers have greater antihypertensive responses to metoprolol
ADRB1	rs1801252	Candidate gene	Caucasians (n=233)	Ser49Ser homozygotes showed a non-significant tendency to have a better response to bisoprolol
ADRB1	rs1801253or rs1801252	Candidate gene	Caucasians (n = 340)	There was no association of the polymorphisms with the blood pressure response to atenolol
CYP2D6	*4	Candidate gene	Caucasians (n= 1533)	* 4/4 * genotype carriers have better blood pressure responses to metoprolol
CYP2D6	*3, *4, others	Candidate gene	Caucasians (n=84)	There was association of the polymorphisms with the blood pressure response to metoprolol
CYP2D6	*2,*3, others	Candidate gene	African Americans (n=84), European Americans (n=125), Asians (n=1) and others (n=8)	There was no association between CYP2D6 variants and blood pressure responses to metoprolol
CYP2D6	rs1065852	Candidate gene	Chinese population (n=93)	There was no significant association between CYP2D6 gene polymorphisms and treatment outcome with metoprolol
CYP2D6	*2, *3, others	Candidate gene	White (n=39), black (n=9) and Latino-Hispanic (n=2) population	There was no significant association between CYP2D6 variants and blood pressure responses to metoprolol
SLC25A31	rs201279313	GWAS	African Americans (n=318)	Heterozygous patients have better antihypertensive responses to ß-blockers
FGD5	rs294610	GWAS	Caucasians (n=201)	A allele carriers have better blood pressure responses to metoprolol
SLC4A1	rs45545233	GWAS	Caucasians (n=434)	C allele carriers have worse responses to ß-blockers
ACY3	rs2514036, rs948445, and rs2514037	GWAS	Caucasians (n=228)	The SNPs rs2514036, rs948445, and rs2514037 are associated with blood pressure responses to bisoprolol
BST1	rs28404156	GWAS	Caucasians (n=1254)	A allele carriers have better blood pressure responses to ß-blockers
KLOTHO	rs36217263	GWAS	Filipinos (n=76)	Deletion of at least one copy of allele A for rs36217263 in the KLOTHO gene is associated with poor response to ß-blockers

2C9 (CYP2C9) genes that are responsible for increased sensitivity to warfarin which poses a greater risk of warfarin induced bleeding. Hence the patients with the aforementioned genetic variants need lesser dosage of warfarin to reach the required therapeutic target than those patients without these gene variants (Lee *et al*., 2014). Patients who carry HLA B*1502 variant of Human leukocyte antigen (HLA) gene are more likely to experience carbamazepine associated Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Likewise, those who carry HLA A*31:01 variant is more likely to experience carbamazepine associated hypersensitivity syndrome (HSS) (Lee *et al*., 2014). Pharmacogenomics has been used to explain why different people respond differently to different medications. This has aided in the alteration of the recommendations for providing the proper dose to the appropriate patient while also preventing potentially fatal adverse reactions (Roden *et al*., 2019; Lee *et al*., 2014).

Advantages of pharmacogenomics. Formulating drugs based on patient's genetic profile analysis will lead to better drug response, reduced possibility of adverse reactions and faster recovery time. Instead of weight and age-based dosage calculation, genetic profile-based dosage method will lead to better evaluation of the correct dose of medicine require by the patient. This would increase the therapy's effectiveness while reducing the risk of overdosing (Aneesh *et al*., 2009) Cost of failed clinical drug trials and compensation in case of adverse drug reactions during clinical studies can be avoided by genetic profiling of patients. This would lead to an overall cost reduction of healthcare due to reduced adverse drug reactions (Health., 2011).

Challenges and limitations in pharmacogenomics. Adverse drug reactions can lead to significant morbidity and mortality amongst the patients. These can cause lifelong health related problems that can hinder the day-to-day life of the affected individuals. Adverse drug reactions hence become a costly affair for the healthcare system and in turn affect the economy of a country. It is therefore important to pharmacogenomicaly characterize the patients. Such a grading system is necessary to be set in place so that the patients at a lesser risk of adverse reactions may receive the sufficient therapeutic effect from the drug and those at higher risk of adverse reactions are prevented from developing severe drug toxicities (Lee *et al*., 2014; Alfirevic and Pirmohamed, 2008).

The incorporation of pharmacogenomics data into clinical practice is a challenging process. It requires that the clinicians be familiar and well versed with the effects of various genes on the response of various drugs which is easier said than done. The adjustment of drug dosages with the incorporation of genetic data is an uphill task which is a genuine reason for the hesitation amongst clinicians regarding taking up this enormous job (Surendiran *et al*., 2008).There are few drug alternatives available for patients. There might only be one or two approved drugs available for a certain condition and there may be no other treatments available for patients with gene abnormalities that prevent them from taking these medications. In order to fully utilize the beneficial aspects of pharmacogenomics, it is proposed that the genetic analysis of the entire population should be done for the polymorphisms found in drug metabolizing enzymes so that the potential adverse drug effects can be successfully avoided. This, although in itself is a major task at hand, it also poses ethical issues in terms of consent for large scale genetic data collection, investment of extensive finances for research that is applicable to a relatively small portion of the population, ownership of genomic testing results as well as the issue of the confidentiality of the genetic information of the people (Gershon *et al*., 2014).

There are certain rare genomic variants for which sufficient data is not available to determine the specific phenotype and hence the possible outcome of drug response remains unpredictable. Also sometimes, a single gene variation can result in multiple drug responses. There is lack of proper laboratory infrastructure and technologies that are required for the smooth conduction of genetic tests and correct evaluation of the test results (Roden *et al*., 2019). The field of pharmacogenomics is dynamic and there is a continuous need to execute extensive research in order to gain new evidence and expand the genomic database to include more and more drugs and genes. The collection of pharmacogenomics data as well the maintenance of these records is a challenging process and a costly affair and hence requires large scale financial and human resources (Roden *et al*., 2019). Dissuasion of pharmaceutical companies in developing several

pharmacogenomic drugs because bringing a drug to market costs hundreds of millions of dollars and new medications that only benefit a small portion of the population is a costly affair for which companies are hesitant.

Pharmacogenomics in the future. Pharmacogenomics provides significant benefits to clinical practice in the present time also have a greater potential to do so in the future. The major research goals for the future in the field of pharmacogenomics are identification of genes and polymorphisms that affect the therapeutic outcome of presently available drugs and the synthesis of specific drugs for specific conditions with the help of these newly discovered genes (Roden *et al*., 2006; Tsai and Hoyme, 2002). By including reproducible and quantifiable end points. It is possible to attain well defined phenotypes with higher chances of predictability of the possible drug response development of new technologies, high output genotyping can be done that will decrease the cost input. It will also decrease the time span between genetic testing and attainment of results (Alfirevic and Pirmohamed, 2008).

Regulation of genotyping tests and the incorporation of the test results in the development of new drugs, as well as the display of the genetic data and instructions on the drug label to inform the clinicians and patients will help in easier understanding and better adaptation (Roden *et al*., 2006). Use of networking for global knowledge sharing and continuing education is a great tool for integration of genetic data with drugs and diseases. Pharmacogenomics research study will help us to understand the way different drugs work in a better way. It will also help in accurate prediction of their safety and efficacy. Establishment of bio-bank that act as a repository for various biological samples will help facilitate pharmacogenomics study by acting as an important database for research (Alfirevic and Pirmohamed, 2008). The demonstration of the results of pharmacogenomics testing, like the better predictability of drug response as well as the better clinical outcome, will help in easier incorporation and adaptation of the benefits of pretreatment genotyping by the clinicians (Alfirevic and Pirmohamed, 2008).The adverse reactions of many drugs suggest underlying genetic causative factors for which pharmacogenomics study and research needs to be undertaken in a well-planned way in order to recognize and understand the genomics and curb the advent of adverse reactions at the grass root level (Lee *et al*., 2014).

Conclusion

Genomic technologies are also progressing at a breakneck pace, close to how computer technology has progressed over the last two decades but it is not known that where genomic technology will be in ten years. The use of sophisticated EHR systems, the incorporation of pharmacogenomic data into routine clinical practice seems to be a promising future prospect. International collaboration is rising, as it is in the rest of the genetics field, resulting in an increase in the patient data accessible for pharmacogenetic investigations. Until now, most of these have relied on observational studies only but now pharmaceutical companies have started to make the data regarding clinical trials public and have also begun the process of inclusion of genetic studies into the trials. As a consequence, there will be more opportunities not only for discovering genetic variants linked to response but also for evaluating pharmacological adverse effects.

Conflict of Interests. The authors declare that they have no conflict of interest.

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