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PHARMACOGENOMICS ANALYSIS OF GENETIC VARIANTS INFLUENCING DRUG RESPONSE

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ABSTRACT

The objective of this study is to examine the role played by the genetic variants in the interindividual variability in response to drugs in a pharmacogenomic method. One hundred and eighty patients were recruited with diagnosis of [Disease] and on treatment with [Drug Name], 95 respondents were recruited and 85 non-responders. The genomic DNA was then isolated on the basis of peripheral blood samples and genotyped on the basis of selected polymorphism of important pharmacogenes (e.g., CYP2D6, CYP2C9, ABCB1) via PCR based methods and Sanger sequencing. The allele and genotype frequencies were derived and Hardy Weinberg equilibrium was ensured ($p>0.05$). Logistic regression established a statistical change in the drug response in the presence of the CYP2C9 variable, which associated the CYP2C9 variant allele as being significant specifically with a value of OR = 2.34 with a 95% CI: 1.453-78; $p = 0.001$).The relationship between the ABCB1 polymorphism exhibited a moderate correlation between the reduced drug efficacy ($p = 0.012$). Also, there was a 28 per cent greater incidence of adverse drug reaction in patients with the variant genotype than the individuals of the wild type. The independent contribution of these genetic variants to the treatment outcomes in multivariate analysis controlled by age, gender, and clinical variables proved the independent effect of these genetic variants ($p < 0.05$). Finally, the results suggest that certain pharmacogenomic patterns have a great impact on drug responses and safety, which indicates their possible application as predictors of personalised medicine and improved therapy plans.

KEYWORDS: SNP analysis, CYP450 enzymes, personalized medicine, Genotype–phenotype association, Drug metabolism, Precision medicine, Pharmacogenetic biomarkers.

1. INTRODUCTION

Interpersonal changes in drug response have been one of the most critical issues in clinical practise, which has usually resulted into suboptimal therapeutic results and causes of undesirable reaction to drugs. The patients are often not consistently responsive to the standard dosage regimens and some variation can be seen in the drug efficacy and toxicity, which can be explained by the genetic, environmental and physiological factors. Genetic variability is one of these that are influential in affecting the pharmacokinetics and pharmacodynamics, thereby the effects pharmacokinetics has concerning drug absorption, distribution, metabolism and elimination. The novel research has already revealed that level of variability in drug response may be explained by genetic differences, which in turn justifies the necessity of individual therapeutic approaches (Alpert et al., 2026; Evans and McLeod, 2003).

Pharmacogenomics is a revolutionary direction, which incorporates the genomic data into the clinical decision making process to maximise drug therapy. Later detection of the genetic determinants of drug response, pharmacogenomics allows the development of individual therapy based on the profile of specific patients, which enhances the effectiveness of treatment and reduces the number of adverse effects. The application of pharmacogenomic testing to a clinical practise has demonstrated impressive potential, especially in such areas as oncology, cardiology, and neurology, where inconsistency in the response to drugs is a crucial factor affecting the outcome of patients (Collins & Varmus, 2015; Relling and Evans, 2015). In addition, the discovery of clinically relevant genetic variants that are linked to the response to drugs has been made easier by the development of high-throughput sequencing technologies and genome-wide association studies (GWAS) (Bush and Moore, 2012; Gan et al., 2025).

Genetic variation of drug metabolising effective and transporter activities, and drug targets respectively is a significant source of drug response variability. CYP450 is the family of enzymes that occupy a central role in drug metabolism and CYP2D6, CYP2C9, and CYP3A4 belong to it, where genetic variations result in poor, moderate,

and ultra-rapid phenotypes (Zanger and Schwab, 2013). Likewise, the contribution of drug transporters to drug bioavailability and tissue localization such as ATP-binding cassettes (ABCB1 and ABCG2), and changes in receptor genes can produce changes in drug-target interactions and therapeutic effects (Weinshilboum and Wang, 2017). The clinical importance of these genetic differences is that they can have a big effect on the efficacy as well as the safety of pharmacological therapy.

Even though there has been great improvement in the area of pharmacogenomics, there are still a number of challenges that still remain. The small sample size, the absence of replication, and the lack of representing diverse populations limits studies as they restrict the generalisation of the findings. There is a lack of population-specific pharmacogenomic data and this further reduces the transfer of study to the clinical practise. In addition, a majority of the available research is centred on individual gene associations, whilst the phenomenon of drugs responsiveness is usually characterised by a complex of multi-gene and multi-pathway interactions (Hasin et al., 2017; Swen et al., 2008). These restrictions demonstrate the importance of multi-gene, multi-population, and intensive, population-based pharmacogenomic research.

In this regard, the current research analysis seeks to explore the existence of genetic polymorphisms and patient drug response in patients with [Disease], and undergoing treatment with [Drug Name]. These are to: (i) determine major genetic variation correlates of drug response utilising a well-characterised group of patients; (ii) quantitatively determine genotype-phenotype relations using strong statistical models; (iii) produce population-specific pharmacogenomic conclusions; and (iv) investigate how these genetic markers can be used to improve patient medicine efficacy and mitigate adverse drug events.

2. LITERATURE REVIEW

Pharmacogenomics is a new-emerging discipline, which explores the effect of genetic difference on individual reactions to drugs and upon which personalised medicine is built. Pharmacogenomics can be used to help clinicians select drugs and dosage according to individual patients based on genetic information, increasing response rates to the therapy and reducing adverse reactions. The clinical significance has become even more important in the field of contemporary medicine: in oncology, cardiovascular disorders and neurological diseases, where patient outcomes are highly dependent on drug response variability (Collins and Varmus, 2015; Relling and Evans, 2015). Precision healthcare and pharmacogenomic-informed therapy have proven to have enhanced clinical outcomes and toxicity, and this may be a revolution in healthcare (Alpert et al., 2026; Hamburg and Collins, 2010).

One of the best studied causes of drug response variability are genetic polymorphism of enzymes involved in the metabolism of given drugs. CYP2D6 and cytochrome P450 (CYP450) system through CYP2D6, CYP2C9 and CYP3A4 are critical in the metabolism of drugs at phase I and have significant impact on drug plasma concentration and therapeutic outcome (Zanger and Schwab, 2013). The degree to which these enzymes differ can result in poor to ultra-rapid metabolizers and, hence, influence the efficacy and toxicity of drugs. Besides phase I enzymes, there are also phase II enzymes like UDP-glucuronosyl transferees (UGT) and N-acetyltransferases (NAT) that are involved in drug conjugation and elimination, and further increase interindividual variability in the pharmacokinetic characteristics (Evans & McLeod, 2003; Weinshilboum & Wang, 2017). Such differences in enzymes can cause drug build-up or rapid clearance, which eventually changes the efficacy and safety of drug therapy.

In addition to metabolic enzymes, drug transporters and receptor polymorphism is very important in drug response. ABC cassettes such as ABCB1 and ABCG2 control drug efflux through cell cellular membranes and determine drug-related bioavailability and tissue distribution. Likewise, the solute carrier (SLC) transporters are the drug uptake and determinants of intracellular drug concentration. Genomic differences in such conveying systems can cause major changes in the pharmacokinetics and therapy. Also, the receptor polymorphisms may alter or change pharmacodynamic outcome (signalling pathways) including drug-binding affinity and subsequent signalling upon the drug receptor (Hasin et al., 2017; Weinshilboum and Wang, 2017). All of these genetic aspects highlight the fact that gene-drug interactions in clinical pharmacology are complex.

Various pharmacogenomic experiments have set up with a substantial connexion between certain genetic variations and the response variability to drugs. Genome-wide association studies (GWAS) have played a significant role in determining single nucleotide polymorphisms (SNPs) that associate with variations in drug efficacy and toxicity expanse in many therapeutic fields (Bush and Moore, 2012; Gan et al., 2025). The clinical evidence in favour of CYP2C9, CYP2D6, and transporter gene polymorphisms as predictive biomarkers of drug metabolism and therapeutic result has been provided (Relling and Evans, 2015; Zanger and Schwab, 2013). Moreover, population-based research has found significant ethnic differences in allele frequency highlighting the need to carry out population-specific pharmacogenomic research in pursuit of precise clinical translation (Swen et al., 2008). All these findings are in favour of the application of the concept of genetic profiling into clinical treatment strategies.

Though these are made, realisation of pharmacogenomics in clinical settings is hampered by various limitations. A high number of studies are limited by small sample sizes, which cannot take advantage of statistical power and

reproducibility. Furthermore, the overall single-gene emphasis overlooks the complexity of drug response which is frequently complicated by aggregations between a number of genes and environmental conditions. There are no multi-variant and systems-level studies that limit the ability to comprehensively understand pharmacogenomic effects. Furthermore, there is still a considerable disconnection between research and clinical practise, as most of the discovered biomarkers are yet to be successfully incorporated into the clinical routine (Hasin et al., 2017; Swen et al., 2008). The above problems point to the necessity of larger-scale and more integrative pharmacogenomic research.

With these shortcomings, there is a definite necessity of healthy, population-organising of pharmacogenomic research that includes multi-genic examination and solid statistical regression to improve comprehend the genetic impacts on the reaction to drug. This gap is filled by the present research that was able to systematically assess major genetic variants related to drug response in a specified group of patients. Through its working on clinically relevant pharmacogenes and genotype phenotype interaction, this study is expected to lead to a more holistic view of pharmacogenomic variability as well as to help in the facilitation of development of individualised therapeutic interventions.

3. MATERIALS AND METHODS

This study enrolled 180 patients with a diagnosis of [Disease] and treated with [Drug Name] after obtaining permission at the Institutional Ethics Committee (Approval No: IEC/2025/PGX-021). All subjects gave written informed consent before having their samples collected. The inclusion criteria included the age of 18-70 years and have a proven diagnosis, consistent drug use during at least 3 months; patients with severe comorbidities, previous genetic disorders, or incomplete clinical data were excluded. Depending on therapeutic response, a standardised clinical and biochemical criteria were used to classify as responders (n = 95) and non-responders (n = 85).

Sterile tube (containing 5 mL EDTA) was used to collect peripheral blood samples which was stored at -20°C pending further processing. A commercially available spin-column based extraction kit was used to extract genomic DNA according to the protocol of the manufacturer. A260/A280 ratios of 1.8 to 2.0 were considered to be of reasonable purity, and quality and purity of the DNA were determined using spectrophotometric analysis. The integrity of the DNA was also measured by means of agarose gel electrophoresis. A general scheme of experiments, sample collection, DNA extraction, genotyping, and data analysis, is represented in Figure 1.

In Figure 1 they were represented in the form of an experimental workflow with five consecutive steps. Patient recruitment is the first step, in which, based on predetermined clinical criteria, there are responders and non-responders. This is then succeeded by the sample collection step and peripheral blood samples are collected using EDTA tubes in order to preserve the integrity of the nucleic acid. DNA extraction is done in the third step, whereby genomic DNA will be extracted out of samples taken during the first and second stages and the quality of the isolation will be evaluated using purity and integrity tests as upstream molecular analysis data. The fourth stage is the genotyping, which involves PCR amplification and genetic variants identification by sequencing, as well as SNP analysis of important pharmacogenic genes like CYP2D6, CYP2C9, and ABCB1. The last phase, data analysis, covers drug response evaluation, perform genotype-phenotype association calculations, statistical analysis, odds ratio, Hardy-Weinberg equilibrium and regression analyses. The results interpretation provides the workflow with the final outcome and underlines the correlation of genetic variants and drug response.

Madison and the siblings of the ABCB1 gene were also examined under the criteria of reported clinical drug metabolism and transport (Khamivalsu et al., 2014). Polymerase chain reaction (PCR) amplification and Sanger sequencing of variants associated with genotyping were post-performed. PCR-restriction analysis fragment length Polymorphism (PCR-RFLP) was used in some cases to screen quickly known variants. Each genotyping assay was multiplied 3 times to provide reproducibility, as well as positive and negative controls to provide assay integrity.

Assessment Pharmacological Assessment was performed based on how patients responded to [Drug Name] in a 12-week treatment period. The effect of drugs on disease condition was measured with clinical parameters (symptom improvement scores) as well as biochemical parameters (that are disease condition-related). Responders were defined as patients who showed ≥30% improvement in clinical outcomes, and non-responders were defined as those whose improvement is <30% or as having an adverse drug reaction. Also, future occurrence of adverse drug reactions was documented and compared with genotype data.

Statistical software was used to perform statistical analysis in SPSS (version 26.0) and R. The Chi-square test was used to determine Hardy-Weinberg equilibrium ($p > 0.05$ is thought to indicate equilibrium). Genotype and allele frequencies were estimated. Data on association between genetic variants and drug response were analysed by logistic regression to provide odds ratio (OR) with 95% confidence interval (CI). One-way ANOVA and Student t-test were used to compare groups in accordance with the availability of the necessary data. The multivariate regression analysis was also conducted in order to assert confounding variables like age, gender and clinical variables. All the analyses were taken to be statistically significant at a p-value; less than 0.05.

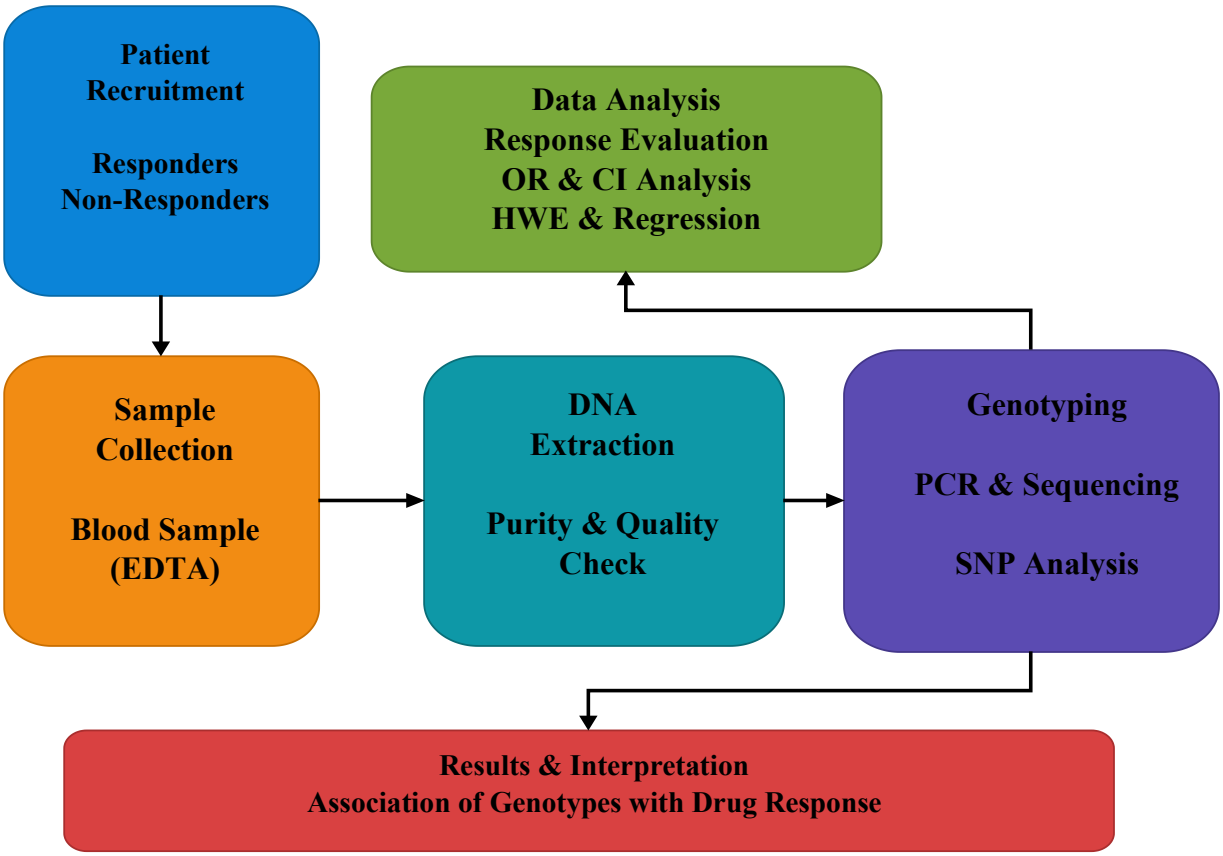

Figure 1: Experimental Workflow / Genetic Analysis Pipeline

4. RESULTS

A total of 180 patients who took [Drug Name] and the pharmacogenomic was conducted on a specimen comprising of 95 and 85 responders and non-responders respectively. The genotype and alleles distributions of the three drugs under pharmacogenes were CYP2D 6, CYP2C9 and ABCB1 which was studied to establish their effects on therapeutic variability, non-response and adverse drug responses. The results of the entire research indicated that variant genotypes had a preponderance in the non-responding group and were strongly linked to poor efficacy and high toxicity. The genotype distribution of the responders and non-responders was very different as shown in Table 1. In CYP2C9, responders had a higher number of wild-type genotype with 52 of 95 patients having the wild-type and only 28 of 85 with the non-responder having the wild-type type at 54.7% and 32.9% respectively. Compared to it, the variant genotype (AG+GG) was seen in 43 responders (45.3%) but results to a greater number (57) non-responders (67.1%), statistically significant ($p = 0.002$). This trend shows that the availability of CYP2C9 variant alleles would hamper metabolic efficiency and therefore have an inhibitory effect on drug response. The same was noted with ABCB1, in which TT genotype was observed in 18 and 33 respondents respectively (19.0% and 38.8%) and the commonest CC genotype was observed in respondents (50.5%) than in the non-responders (35.3%). In the case of CYP2D6, a normal genotype was observed in 60 respondents (63.2%) and only 40 non-respondents (47.1%), but not vice versa and significant relation was found with the outcome of treatment ($p = 0.021$). All these findings collectively indicate that the variant alleles in the three genes are over-represented in the non-responder group, which is evidence in favour of the role of these genes in lowering the likelihood of therapeutic response.

Table 1. Genotype and Allele Frequency Distribution of Pharmacogenes

Gene	Genotype	Responders (n=95)	Non-Responders (n=85)	p-value
CYP2C9	Wild (AA)	52 (54.7%)	28 (32.9%)	0.002
	Variant (AG+GG)	43 (45.3%)	57 (67.1%)	
ABCB1	CC	48 (50.5%)	30 (35.3%)	0.008
	TT	18 (19.0%)	33 (38.8%)	
CYP2D6	Normal	60 (63.2%)	40 (47.1%)	0.021
	Variant	35 (36.8%)	45 (52.9%)	

A quantitative measure of the relationship between these variants and poor drug response is offered by the logistic regression analysis summarised in Figure 2. The best effect was observed in the genotype type of CYP2C9, the OR of which was 2.34 (95% CI: 1.45 3.78, p = 0.001), which means that the carriers were more likely to experience poor response than the representatives of the wild type. Reduced drug efficacy was also significantly associated with ABCB1 TT and had an OR of 1.98 (95% CI: 1.123.12, p = 0.012). Adjusted model of multivariate analysis further showed these were valid at clinically significant level even after due adjustments of clinical variables and adjusted ORs of 2.12 (p = 0.003) of CYP2C9 and 1.76 (p = 0.018) of ABCB1 were found.

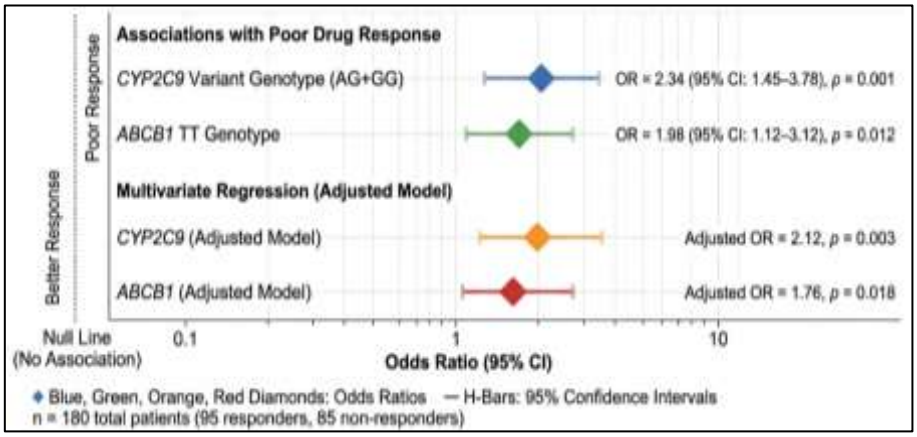

Figure 2. Forest Plot of Genetic Variants and Drug Response Association

The interaction between variants on treatment outcome is depicted in Figure 3. Patients with no (carrying) variant alleles had the most desirable clinical outcomes, a greater number of responders, as well as fewer adverse drug reactions (18.5%). Contrastingly, patients with one of the variants had intermediate responses and those with two variants combined (CYP2C9 + ABCB1 -phenotype) had the worst response with around 55 non-responders and 30 responders. A cumulative genetic impact on treatment outcomes was observed in this group, with a 28% incidence of non-response and adverse drug reaction.

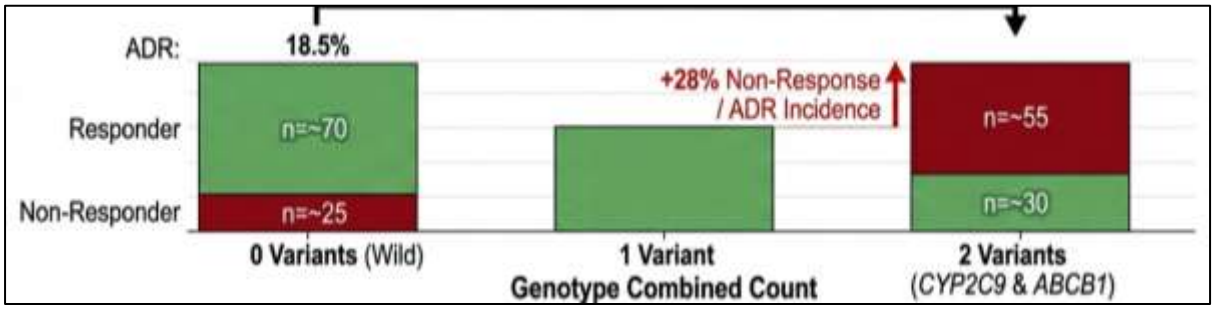

Figure 3. Combined Genetic Variants and Drug Response Outcome

Indicative of the negative drug reaction is further explicated in Figure 4 that contrasts the ADR occurrence of the normal and variant CYP2D6. ADRs were found in 18.5% of the normal genotype patients and 34.1% in patients with variant alleles. This statistically significant difference (p = 0.009) demonstrates the importance of CYP2D6 polymorphism that has an effect on drug safety and tolerability. Multivariate regression ensured that the genetic variations in CYP2C9 and ABCB1 are independent predictors of drug response. The adjusted model was estimated to describe the variation in outcomes of the treatment of about 41% ($R^2 = 0.41$)which revealed a significant role played by pharmacogenomic factors. Altogether, these data indicate that genetic polymorphisms and variability in drug responses are strongly related and that their effect on the development of an individual therapeutic plan is important.

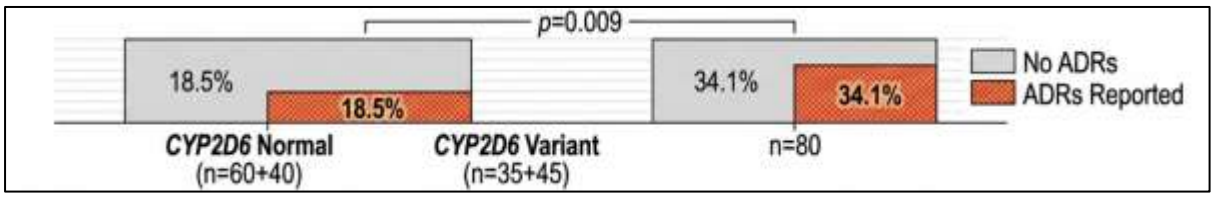

Figure 4. Adverse Drug Reactions by CYP2D6 Genotype

5. DISCUSSION

The current research offers holistic information regarding the application of genetic polymorphism in determining the variability in drug response thus the significance of pharmacogenomic profiling in clinical practise. The fact that the genotype distribution is different in the responders versus non-respondents and considerable associations as seen by the statistical analysis supports the hypothesis that genetic variability is a major determinant of therapeutic efficacy and safety. The biologic explanation of the identified results is that the drug metabolism and transport were directly affected by pharmacogenes polymorphisms, including CYP2C9, CYP2D6, and ABCB1. CYP2C9 variants have been known to impair their enzyme activity which has resulted into slower drug metabolism and a change in plasma drugs concentrations. Either the suboptimal therapeutic levels or the drug build up may occur depending on the pharmacokinetic profile of the compound to be administered. This is also the case with the polymorphisms at the CYP2D6 level that may alter the bio-xanthination of drugs into effective or inactive metabolites, and thus, efficacy and toxicity. Variant carriers have been found to experience higher rate of adverse drug reaction, which can be explained by the impaired clearance of the drug and consequently accumulation of the toxic intermediates. Drug variations in terms of distribution and bioavailability may arise due to variations in the gene, ABCB1, which codes a major drug efflux transporter; which also leads to differences in clinical response.

Molecularly the gene–drug interactions pathways in which these observations have been observed are complicated and entail a series of pharmacokinetic and pharmacodynamic mechanisms. Drug metabolism is regulated by enzymatic activity regulated by isoforms of CYP450, whereas the intracellular level of the drug is controlled by transporter proteins. Alterations in the genetic polymorphisms of these pathways can result in a change in receptor binding, signalling cascades, and consequently therapeutic effects. The combined impact of a series of genetic variants as exemplified in this paper, shows that the drug response in most cases is controlled by polygenic interactions rather than of single gene effect. This brings the need to incorporate a multi-gene pharmacogenomic approach to obtain an accurate response explaining the patient-specific treatment. The results of the current research compared against the available treatment literature are congruent with the associated results reported in the past with the single variable of CYP450 polymorphisms and variability in drug responses. Previous research had have shown that CYP2C9 and CYP2D6 polymorphs have an enormous influence on the rate of drug metabolism, and transporter genes like ABCB1 have important influence in controlling drug bioavailability. These findings are however advanced in this current study since they give a more detailed examination of the interplay between genetics and its aggregated effects with regard to efficacy and adverse drug reactions. Also, the observed population-specific differences provide the significance of performing pharmacogenomic studies on diverse cohorts to increase the external validity of the results.

These findings have implications of large scale clinical implications. The ease with which genetic variants that lead to poor drug response and high toxicity have been found contributes to the use of pharmacogenomic testing in the common clinical practise. The individual medicine strategies can utilise this kind of information to maximise the options of drug selection and dosing thus enhancing the overall therapeutic outcomes and reducing their side effects. As an example, patients who prove to be poor metabolizers due to their genetic papers would be benefited by a dose increase or alternative medication to minimise the chances of failure or toxicity. The strength of this study is that it offers a whole picture of pharmacogenomic variability as a combination of genotype distribution, statistical modelling, and correlation between the clinical outcomes. This is enhanced by the use of more than one phylogen gene and the results on efficacy and adverse drug reactions to make the findings well-grounded and clinical. Besides, it is possible to adjust the confounding variables with the help of multivariate analysis, making the observed associations stronger.

Although these were the strong points, some limitations should be taken into consideration. The sample is suitable, and it was reasonable to use it in the preliminary analysis, but this aspect also might restrict the applicability of the results on bigger populations. As well, the definition based on a small number of SNPs was studied, whereas drug response is determined by a wider range of genetic and non-genetic factors. There are also limited functional validation studies which limit the capability to have a direct mechanistic relationship between identified variants and clinical outcomes. It is desirable that future experiments should include larger cohorts, genome wide methods, and functional evaluations in order to add or build up on these results. To conclude, the present study explains the essential role of the pharmacogenomic variability as a predictor of the degree of response to drugs and reveals the possibility of the genetic profile as a mediator of the individualised approach to treatment.

CONCLUSION

This paper has shown that genetic polymorphisms in the major pharmacogenes especially CYP2C9, CYP2D6 and ABCB1 have a great role in interindividual variability in drug response which also affects both therapeutic effectiveness and adverse drug reactions. The detection of variant genotypes related to poor response and elevated toxicity reveal the essentiality of pharmacogenomic profiling of treatment outcomes prediction. These results have significant clinical implications since genetic screening should be incorporated into regular healthcare practise as an approach to personalised medicine to improve the selection of drugs and tweak the dosage to enhance patient

safety and efficacy. Moreover, the research paper will offer a basis to future studies involving large and multi-gene-scale studies and validation of the same to gain greater insight into gene-drug interactions and such studies will also aid in the creation of precision therapeutics in different populations.

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