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The role of genetic variations in drug metabolism and their impact on therapeutic outcomes

[1]Jeetendra Kumar Prajapati and [2]Aman Shukla

[1]Lecturer, Department of Pharmacy, Mahakaushal University, Jabalpur, Madhya Pradesh, India
[2]Assistant Professor, Department of Pharmacy, Mahakaushal University, Jabalpur, Madhya Pradesh, India

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Corresponding Author: Jeetendra Kumar Prajapati

Abstract

Medication interactions have been the focus of most prominent pharmacogenomics studies used in the medical field. Its effects on therapy and medication discovery are substantial. For treatment to advance, pharmacogenomics must be widely used. The complex role that genes play in determining how the body responds to drugs is the primary area of study. New advances in clinical treatments have led to the discovery of novel biomarkers that may be used to categorise patients according to their likelihood of responding to a certain drug. The goal is to enhance personalised treatment by ensuring that the correct medication is administered at the correct time in the correct amount and that the correct prescriptions are given. Variation in drug response between individuals is caused by a myriad of factors, including genetics, the environment, and the patient themselves, all of which influence the pharmacokinetics and/or pharmacodynamics of drugs. Pharmacogenomics influences drug development, disease susceptibility, and treatment effectiveness. To provide the groundwork for future pharmacogenomics applications, methodologies, or tactics, this study aims to provide a review.

Keywords: Pharmacogenomics, genetic approach, drug therapy, drug development, personalized medicine/therapy, human diseases

Introduction

While doctors have known for a long time that people react differently to drugs, it wasn't until 1957 that Arno Motulsky offered the hypothesis that "...hereditary gene-controlled enzymatic factors determine why, with identical exposure, certain individuals become'sick,' whereas others are not affected" based on research on drug response variations. Two years down the road, Vogel was the first to use the word "pharmacogenetics" to characterise the link between heredity and drug reactions. Technological progress in molecular genetics has led to a better understanding of the DNA sequence that codes for these enzymes and how variations in that sequence affect their activity, while developments in biochemistry have led to the identification of drug metabolising enzymes and the characterisation of the reactions they catalyse.

Pharmacogenetics seeks to use genetic information for the purpose of predicting therapeutic response and customising medicine administration. A new trend in the field of pharmacogenomics is to examine the whole genome for connections with pharmacologic phenotypes, as opposed to the older practice of analysing polymorphisms within one or more candidate genes (pharmacogenetics). Converting prodrugs into active molecules or drugs into harmful metabolites are other possible outcomes of drug metabolism, in addition to the more common processes of making drugs more water-soluble and excretable. This historical categorisation does not necessarily reflect the order of reactions in drug metabolism, even though there are two pathways of metabolism: the phase I reactions (oxidation, reduction, and hydrolysis) and the phase II conjugation reactions (glucuronidation, acetylation, sulfation, and methylation). All of these reactions lead to the same end: the excretion of hydrophilic metabolites from lipophilic medicines.

A growing number of genetic variations influence how drugs are processed in the body and how the body reacts to them. The effect of genetic diversity on a medication's therapeutic index is becoming more and more apparent to clinicians. Although many drug-metabolizing enzyme connections have been found, we will only be covering the drug-variant pairings that doctors should be paying close attention to right now.

Literature Review

Afsar, Nasir *et al*. (2019) [1]. Drug responsiveness may be impacted by genetic variations in transporters and enzymes that metabolise drugs. There are consequences for the optimal selection and dose of different medications in different populations due to the large variation in frequency among races. At this time, there is no description of the distribution of genetic polymorphisms in healthy Pakistanis. A total of 155 people, including 98 females, were surveyed throughout all districts of Karachi for this research. Saliva DNA was genotyped for SNVs in certain genes, including CYP1A1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5, in addition to ALDH3A1, GSTA1, ABCB1, but also ABCC2. A little over two-thirds of the people who took part were born to parents who had no blood relation. Variant alleles of CYP450 1A2, 2B6, 2C19, 3A5, ALDH3A1, GSTM1, ABCB1, and ABCC2 were more common in this research group compared to other ethnicities reported in the HapMap database, with a typically higher frequency (p<0.05). On the other hand, GSTA1 had a decreased frequency of variant alleles. Thus, compared to other ethnicities, the Pakistani population sample from Karachi showed a considerably different prevalence of variant drug metabolising enzymes and ABC transporters. This difference might have potential therapeutic implications for the effectiveness and safety of drugs.

Schärfe, Charlotta *et al*. (2017) [2]. In clinical practice, we see a wide range of medication effects and efficacies. There is a lot of knowledge on the amount of genetic variability in classic pharmacokinetic genes, but less about the impact of genetic variation in pharmacological targets. We conducted a comprehensive computational investigation of the frequency of functional variations in 806 drug-related genes, including 628 known drug targets, using 60,706 human exomes from the ExAC dataset. In addition, we calculated the probability that functional variations in the targets of 1236 FDA-approved medications would be present in both the overall ExAC population and several geographic sub-populations. It is very unlikely that clinical trials would detect the majority of genetic variations in drug-related genes since they are extremely infrequent (f < 0.1%). We also demonstrate that patient risk differs across a wide range of medications and according to their geographic origin. Based on a focused analysis of oncological drug targets, it is highly probable that both somatic alterations and germline variants carried over into the tumour genome could impact the response to antineoplastic agents (44% probability). The results of this research show that 40% of individuals probably have a variation that might have functional impacts on a target for routinely used medications, even though most variants are so uncommon that they are probably not seen in clinical trials. The effectiveness of drugs may be affected by these variations.

Arshad, Shumaila *et al*. (2018) [3]. We still don't fully understand the role that genetic variants in drug metabolism genes play in the observed inter-individual heterogeneity in medication response. Pharmacogenetics is the branch of genetics that studies how different people react to drugs differently. A variety of variables may affect how medications are metabolised, which in turn affects how those drugs are responded to. This article gives a general outline of how genetic variants impact a drug's reaction. The cytochrome P450 enzyme system is a superfamily of enzymes that metabolises a wide variety of endogenous and medicinal compounds, as well as many pharmaceuticals used in clinical practice. In most cases, there are two distinct reactions that comprise metabolism: phase I and phase II. Phase I responses are where CYP450 is most often seen. The enzyme system plays a pivotal role in half of the removal of medicines and over 80% of their oxidative metabolism.

Ali, Rojgar H. (2020) [4]. Since pharmacokinetic and pharmacodynamic processes are both influenced by genetic variances, it stands to reason that medication responses would also vary from one person to the next. The VKORC1 gene, which codes for the active sites of the vitamin K epoxide reductase enzyme, is an example of a gene that may be mutated to impact medication targets (pharmacodynamics). As an example of a pharmaceutical whose pharmacodynamic qualities have been altered by mutation, the anticancer drug irinotecan is well-known. It is well-known that this medication may inhibit bone marrow. An abnormality in the UDP-GT 1A1 gene may explain why this adverse medication response is more severe in some people than in others. Better future medication targeting may be possible with the identification of certain genes. It is worthwhile for drug authorities to fund pharmacogenetic testing and personalised medicine because they increase the therapeutic window for better treatment approaches, decrease the rate of toxicity and the dosage of the drug, save lives, and improve future clinical practice in an efficient and effective manner.

Sileshi, Tesemma *et al*. (2022) [5]. A new family of antibiotics called rifamycins has just gained clinical approval for use in the treatment of TB. The pharmacokinetics of these substances might vary greatly from one person to another. The purpose of this comprehensive study is to show how rifamycin pharmacokinetics differ from one person to the next due to genetic differences in drug-metabolizing enzymes and transporter proteins. As stated in the PRISMA declaration, we adhered to all of their recommendations. Scopus, Web of Science, PubMed, and Embase were combed through to find applicable studies. We only considered studies that reported how rifamycin pharmacokinetics were affected by single nucleotide polymorphisms in drug transporters and metabolising enzymes. Data extraction was carried out separately by two reviewers. Fifteen papers out of 117 that met the requirements were considered for inclusion in the final data synthesis. Pharmacokinetic parameter variability in TB patients is attributable, in part, to single nucleotide polymorphisms in the following genes: SLCO1B1 rs4149032, rs2306283, rs11045819; ABCB1 rs1045642; AADAC rs1803155; CES2 c.-22263A>G (g.738A>G) for rifampicin; and AADAC rs1803155 for rifapentine and AADAC rs1803155 for rifapentine. Variation in drug-metabolizing enzymes and transporters affects the pharmacokinetics of rifamycins. The only way to prove these associations, however, is via randomised clinical trials.

Genetic causes of individual variability in drug response

Pharmacological response, toxicity, and phenotypic variability all vary greatly, making it impossible to employ a

medicine in a clinical environment (Figure 1). Even with the most cutting-edge medications, only about 70% of patients report a positive reaction, and many more have unwanted side effects. There is a poor risk-benefit ratio for a lot of patients because of this. The fields of pharmacodynamics (PD) and pharmacokinetics (PK) provide quantitative evaluations of drug exposure and effect, and a grasp of these areas is necessary for comprehending variability. While pharmacokinetics focusses on ADME (absorption, distribution, metabolism, and excretion), pharmacodynamics is more concerned with drug targets (receptors and enzymes), downstream signalling pathways, and pharmacological response. Important for PK-PD are a number of polymorphism genes. Because the ADME controls the amount of medicine that reaches the bloodstream, measuring drug levels provides phenotypic markers that may inform personalised treatment plans. In the past, PK screening made use of high-throughput technology to identify potential cancer treatment toxicity or effectiveness indicators. Individualised therapy tailored to each patient's unique genetic makeup could be possible with the use of these biomarkers in clinical practice. Improving patient safety via the identification of biomarkers linked to drug metabolism for customised therapy is a potential outcome of pharmacogenomic screening and the practical usefulness of pharmacogenomic technology. Although pharmacogenomic studies were carried out in adult cohorts, pharmacogenetic research in paediatrics has shown promising results. There are significant adverse pharmacological effects associated with polymorphic drug-metabolizing enzymes, as shown in a meta-analysis. Protein therapies include a broad spectrum of biologics, including antibodies, fusion proteins, therapeutic replacement enzymes, and therapeutic replacement proteins. Cancer, inflammatory, autoimmune, respiratory, vascular, and neurological diseases have all seen significant improvements in treatment since their inception because to these innovations. There has not been nearly enough research into the ADME (absorption, distribution, metabolism, and excretion) aspects of protein therapies, despite the fact that these agents are often the focus of *in vivo* pharmacodynamic, effectiveness, and pharmacokinetic studies. To facilitate drug R&D processes leading to the development of safer and more effective biotherapeutics, it is crucial to characterise and investigate their ADME properties in great detail. This is a possible strategy to lessen the likelihood of unsavoury results when using genetic data.

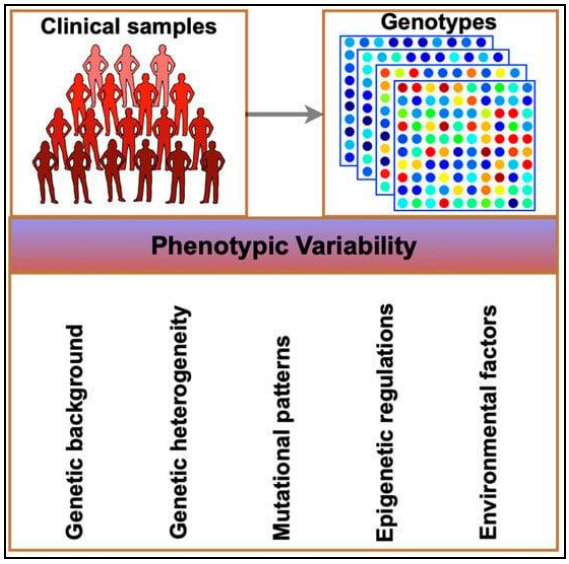

Fig 1: Factors associated with phenotype variation

Several hundred genes encode drug transporters, which are involved in ADME and drug targeting extensively. A variety of functional polymorphisms seem to change pharmacological responsiveness, however their consequences are poorly understood. Examining the consequences of variations in the genes that code for drug receptors is very challenging. Some mutations may be an exception to this rule; for example, those that affect tyrosine kinases, which play an essential role in cancer progression, might be considered activating. For instance, although activating EGFR mutations are often associated with gefitinib sensitivity, imatinib sensitivity is conferred by constitutive activation of the fusion protein BCR/ABL, which occurs as a consequence of chromosomal translocation in leukaemia. The effectiveness of herceptin therapy in treating breast cancer depends on the over-expression of ErbB2.

Future of genotypes in drug therapeutics

If getting the finest pharmacological treatment might have catastrophic results due to a strong and frequent genetic component, prospective genotyping could be recommended. In many instances, reducing the chance of major side effects may be as simple as finding the genetic variables driving varied medication reactions. Human genetic data lends credence to the treatment theory, increasing the drug's chances of success in clinical trials. Common and unusual illness genetics generate a large number of alleles with different effect sizes; these alleles may be used to predict how a medicine will work in a certain situation. Huge population databases and whole genome sequencing have lately made a plethora of human genetic information accessible, which aids in the selection of treatment targets. As the number of phenotypes profiled increases and more alleles from individuals throughout the globe are

discovered, these approaches will become more influential at various stages of a drug development program. Various viewpoints on the topic of prospective genotyping have been expressed in this case due to the fact that genotyping at a therapeutic institution raises not only legal but also financial and practical challenges. On the other hand, serious harm may be avoided with careful monitoring of white blood cell level. There are obviously medical, ethical, legal, and financial considerations to make when implementing possible genotyping at the bedside.

Summary of Computational Approach in Pharmacogenomics and Drug Development and Therapeutics

Mathematical models of population dynamics and treatment responses may help in determining the best times to administer drugs, which has a significant effect on the efficacy of cancer treatments. Nevertheless, bioinformatic processing and proper interpretation of ever-increasingly complicated multi-omics data sets pose a significant obstacle. Protein activity, posttranslational modification, random events, changes in the coding sequence or gene expression, and other short-lived reactions to environmental inputs all have a significant impact on how biological networks function. It is thought that research and medication development cannot be adequately accomplished just via the use of genomics. To better understand the biology of diseases and drug-response phenotypes, it is possible to combine patient histories with several one-dimensional biomolecular-omics data sets using an integrated systems pharmacy method. Ultimately, this approach should result in the identification of novel therapeutic targets. Both Table 1 and Table 2 detail the primary resources, methods, and applications. Figure 2 also provides a summary of the integration of multi-omics data. Methods for the integration of multi-omics data have been proposed by Ritchie M.D. *et al*., and they may be best suited for pharmacogenomics and tailored treatments.

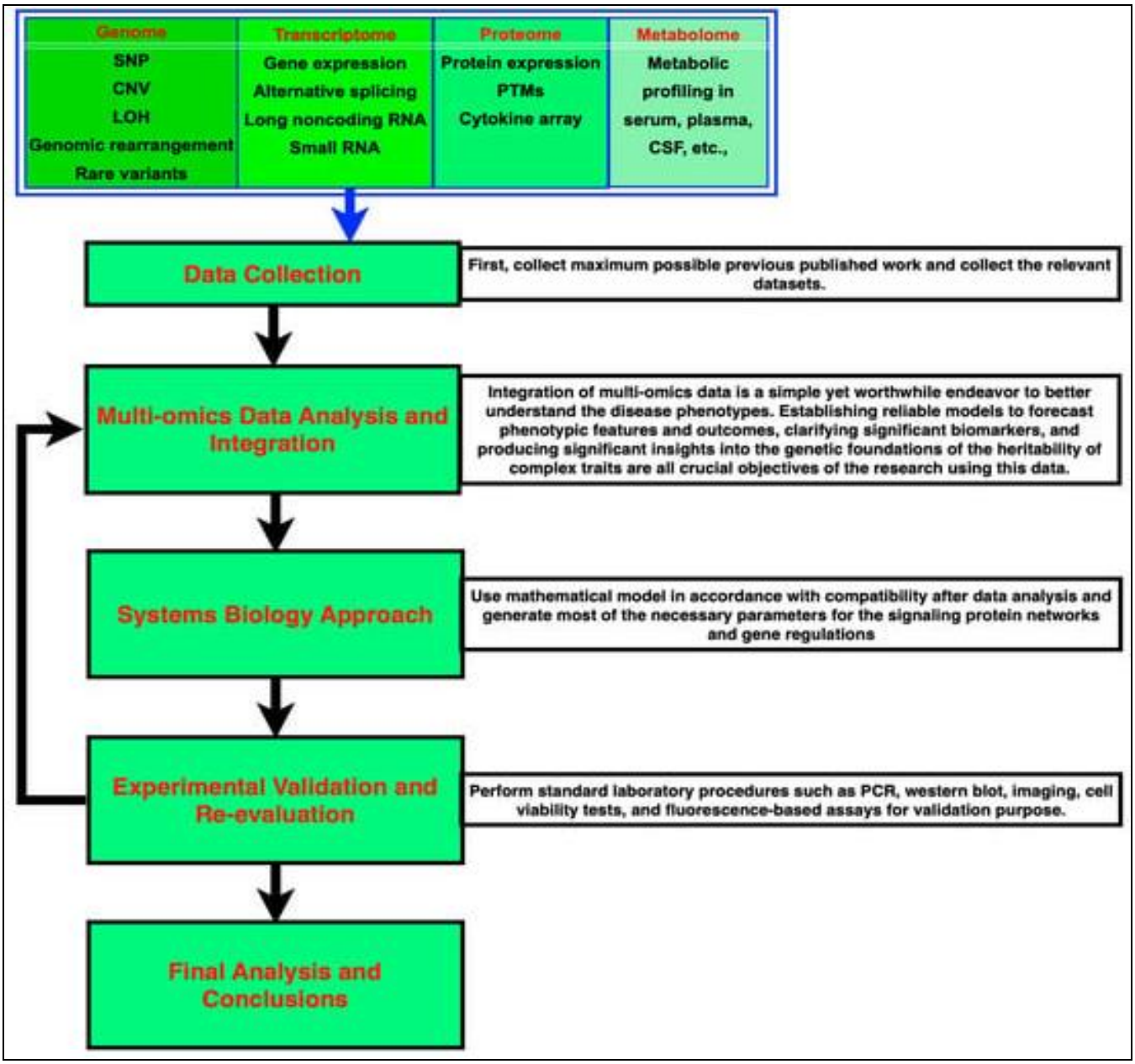

Fig 2: A summary for computational application showing multi-omics data integration and analysis

Overcoming the obstacles of adopting this kind of work in clinics is crucial if the cancer community is to realise the full potential of this approach. Medications have unexpected side effects in around 50% of individuals. A considerable amount of these interindividual differences may be explained by heritable characteristics, and there is mounting evidence linking genetic variants to pharmacological response patterns. The genomic landscape of pharmacogenes is very complex, including tens of thousands of rare variants. The lightning-fast advancements in next-generation sequencing technology have shown this to be true. Because these rare changes are present in every single person, it stands to reason that they contribute significantly to the heritable variety in how drugs work from one person to the next. Understanding the functional importance of variants is the main difficulty now that the problem is too large to allow for a comprehensive experimental characterisation of these variations. This article provides a synopsis of the main points and recent developments in computational prediction methods for understanding the effects of amino acid sequence alterations on drug metabolism-related transporters and enzymes. Nowadays, everyone knows that new findings on the functional effects of non-coding changes, such those to splice sites, regulatory regions, and miRNA binding sites, might be useful for creating treatments based on genetics and pharmacogenomics. We anticipate that the interdisciplinary approach will provide a useful set of tools for incorporating a broad range of unique genetic variability into drug response predictions within a precision medicine framework.

This is why, in the absence of practical experimental methods, computer prediction algorithms are often used to assess the functional effect of genetic variants. The main goal of most of these algorithms is to predict the functional impact of changes that would alter an amino acid sequence. Nevertheless, our knowledge of non-coding mutations that affect splice sites, enhancers, promoters, or miRNA binding sites has recently made significant strides. Below is a rundown of all the traits that computer prediction systems can measure right now. The relevance of numerous traits and features, including RNA binding protein, non-sense-mediated decay, intronic splicing enhancer/silencer, and exonic splicing enhancer/silencer, is dependent on whether genetic variations are located in the gene's coding sequences, untranslated sections, putatively regulatory sequences, or inside introns.

The majority of prediction tools use the relevant evolutionarily conserved sequence as a basis for their judgements. It is common practice to train prediction algorithms on sets of hazardous variants. One distinctive feature of pharmacogenes is their lack of association with human disease and their low level of evolutionary conservation. The comprehension of pharmacogenetic differences is muddled by these variations. We also examined computational approaches for the functional interpretation of genetic variants in this case, with a focus on their usefulness for pharmacogenetic predictions. Our research led us to believe that creating computational tools that can evaluate a person's pharmaco-genotype functionally remains one of the most important areas for therapeutic application of NGS-based genotyping. Figure 2 is an overview of the therapeutic investigations that have been conducted using pharmacogenomics.

Table 1: Essential fundamental methods for pharmacogenetics and genomics genotype analysis.

Method	Short Description and Purpose
Sanger dideoxy (end terminal) sequencing	Analyzing DNA sequences and finding novel polymorphisms.
Denaturing high performance liquid chromatography (DHPLC)	Ion-pair reverse-phase HPLC can be used to differentiate the differentially shaped hybrid molecules (homoduplex versus heteroduplex) that result from the combination of variant and wild-type DNA in order to detect polymorphisms.
PCR-RFLP	Restriction endonucleases, which are enzymes unique to a certain sequence, cut the amplified polymorphic genomic area. The resultant fragments are indicative of the genotypes and are subjected to electrophoresis analysis.
Pyrosequencing [89,90]	A DNA sequencing technique that makes use of the sequencing by synthesis concept. It is used in DNA methylation studies and SNP genotyping. The “next generation” of large-scale DNA sequencing, which can sequence more than 100 million base pairs a day, is based on the same premise as this approach.
Single-base (primer) extension (also known as mini-sequencing) [91]	The 3’ end of short oligonucleotides is annealed directly upstream of the polymorphism site. A combination of (fluorescently labeled) ddNTPs without dNTPs is used to elongate a single base alone. The MALDI-TOF detection technique or sequencing can be used to identify the products. It is used as a multiplex reaction for genotyping SNPs.
DNA microarrays [92]	Using microarray solid-phase attached DNA molecules, a single sample may be genotyped for many SNPs—up to a million—at once. This method is utilized in research on genome-wide associations.
RNA/cDNA microarrays [93]	Utilized to measure the quantity of transcripts in a single sample or to compare two samples while performing gene expression analysis. Beneficial for quantifying a large range of distinct transcripts in a single sample, including those found throughout the genome.
PCR [93]	PCR is a fundamental method used in nearly all modern genomic and pharmacogenetic analyses.
qPCR [94]	Employing different fluorescence quenching or fluorescence energy transfer techniques to detect the development of the PCR product while the PCR reaction is ongoing in order to genotype individual SNPs in a variety of samples.
qRT-PCR [94]	Used following a reverse transcription procedure to measure the number of transcripts in a sample. Helpful for quantifying RNAs in large quantities of samples.

Table 2: Bioinformatics databases and software tools for pharmacogenetics and genomics.

Aim	Computer Solution	Website [Accessed on 3 July 3024]
Databases		
Human genome [87]	National Center for Biotechnology Information in the USA (NCBI)	www.ncbi.nlm.nih.gov/genome/guide/human/
	Ensembl	www.ensembl.org/Homo_sapiens/
SNP databases [96,97,98,99,100]	dbSNP at NCBI	www.ncbi.nlm.nih.gov/snp/
	Japan database JSNP	https://dbarchive.biosciencedbc.jp/data/jsnp/LATEST/README_e.html
Pairwise linkage disequilibrium and haplotypes	HapMap project [101]	www.hapmap.org
Gene expression analysis	Gene Expression Omnibus (GEO) by NCBI [102,103]	www.ncbi.nlm.nih.gov/geo/
Metabolic pathways	Kyoto Encyclopedia of Genes and Genomes (KEGG) [104]	www.genome.jp/kegg/
Software		
Homology search	BLAST at NCBI [105]	www.ncbi.nlm.nih.gov/BLAST/
Sequence alignment and identification of new SNPs	Gap5 (part of Staden package) [106]	http://staden.sourceforge.net/
Haplotype mapping (phasing)	Phase, Fastphase [107,108]	http://stephenslab.uchicago.edu/software.html (there is also a new program for imputation of analyzed to in silico linked SNPs)
Pairwise linkage disequilibrium and visualization of Haplotype blocks	Haploview [109,110]	www.broad.mit.edu/mpg/haploview/
Extended haplotype homozygosity (EHH)	Sweep [111]	www.broad.mit.edu/mpg/sweep/
Analysis of SNPs affecting promoter function	TRANSFAC [112,113]	https://bioinformatics.umg.eu/
Analysis of SNPs affecting splice sites and ESEs	Automated Splice Site Analyses (Children's Mercy Hospitals Missouri, USA) [114]	http://isplice.cmu.edu.tw/index.htm
	ESEfinder 3.0 (Cold Spring Harbor Laboratory) [115]	http://rulai.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home

Sequence analysis, predictions, and functional impact of variants

The degree of conservation indicates the significance of a sequence for the structure and function of the gene product it is connected with. Analysis of the dynamics of evolutionary variation in DNA or amino acid sequences among homologs allows for its computation. Slowly developing, or conserved, sequences exhibit selection pressure against variation in these locations and, as a result, undesirable outcomes in the case of a mutation; in contrast, sections with high evolutionary rates are believed to be pivotal. Most computational prediction methods employ evolutionary conservation as a criterion to differentiate between benign and hazardous variations. Although there are methods that prioritise alignments of nucleotide sequences or a mix of the two, the majority of systems that aim to evaluate missense mutations functionally use alignments of amino acid sequences. While missense variant analysis has shown promise with amino acid sequence alignment, genomic sequence alignments offer greater leeway and enable functional interpretations to be extended to non-amino acid sequence variant classes, like synonymous and regulatory variants. It should be noted that sequence interdependencies are disregarded by the frequently used conservation-based function-dependability predictions. The benefit of combining variation interaction data with conservation-based functionality predictions has recently been shown, however, since improved predictive accuracy may be achieved with the explicit incorporation of residue dependence information from different sequence alignments.

A key function of microRNAs is to control the translation and stability of messenger RNAs. The 3′-untranslated regions (UTRs) include conserved miRNA binding sites, where at least 10% of all SNPs are found. These locations facilitate interaction between miRNA and mRNA and may impact the complementary miRNA-mRNA pairing process. Also, research has shown that microRNAs (miRNAs) have a major impact on the way ADME genes are expressed. Determining the fate of the associated transcript relies heavily on the functional interpretation of genomic alterations inside miRNA target sites. To assess the possible importance of genetic variations in UTRs, many databases provide useful tools, such as MirSNP and the polymiRTS Database 3.0. The databases provide a compilation of SNPs and indels that have been verified experimentally in the miRNA target sites and the miRNA seed regions that bind mRNA. In addition, there are a number of other available methods that may be used to forecast the effect of SNPs.

If there is no experimental proof for a particular mutation, many computational approaches may be employed to predict the likelihood of miRNA-mRNA pairing disruption.

Both MicroSNiPer and ImiRP compare mutant 3′-UTR sequences using large variation databases to detect and predict such disruptions. Similarly, mrSNP can predict how any mutation discovered in NGS-based investigations would affect the miRNA-target transcript relationship. Notably, a large percentage of miRNA target predictions seem to be false-positive, suggesting that studies using miRNA-target databases without robust experimental validations may face comparable problems. Several online tools make it easier to conduct inverse approaches, which analyses changes in miRNAs or pre-miRNAs for possible negative effects and assess the impact of genetic differences in miRNA target sites that are suspected. For a more comprehensive set of variant interpretation tools related to miRNA, the reader is encouraged to consult up-to-date reviews and online resources. The influence of changes in the upstream RNA-binding region (UTR) on RNA-binding protein (RBP) binding, translational efficiency, and ribosomal loading is currently one of many state-of-the-art methods that extend beyond miRNA binding site prediction.

Conclusions

Pharmacogenomics has the potential to be a useful tool for the pharmaceutical industry. In medical history, it is a watershed moment. Some of its main objectives include developing pharmacogenetic patient profiles to predict disease risk and treatment response, enhancing efficacy, discovering novel targets for revolutionary pharmaceuticals, and decreasing adverse drug reactions. In the past, while designing drugs, the whole population was taken into account rather than individual individuals. In contrast to this trend, pharmacogenomics aids in therapeutic focus, increases pharmacological effectiveness, and decreases undesirable effects. In pharmacogenomic therapy, the patient's genotype is the primary focus rather than the disease's outward manifestation, or phenotype. Ultimately, the process will combine pharmacogenomic research to reduce the cost of medicine development. In addition to ensuring the clinical trial is safe, it will reduce the frequency of failures. This means that many potentially useful drugs will not be discarded because of the effects on the study's outliers when pharmacogenomic research is used in the future.

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