Pharmacogenomics

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Abstract

Individual drug response will be better understood thanks to pharmacogenomics, the application of genomic techniques to the study of pharmacological function, drug disposition, and drug action. This serves as the primary foundation for the trend toward more individualized medicine, or "personalised medicine.". Pharmacogenomics-based drug development appears to have a bright future. Lead compounds from preclinical pharmacogenomics testing will ideally be selected based on the fact that they are metabolized and eliminated by multiple alternative pathways. The general idea of pharmacogenomics and its significance in the modern world form the basis of the current review.

Keywords: *Pharmacogenomics; genetic testing personalised medicine*

Introduction

Pharmacogenomics, which involves using genomic techniques to study how drugs work in the body, will help us understand how different people respond to medications. This is the primary foundation for a shift towards personalized medicine, which is often referred to as individualized medicine. To provide a clearer understanding of how pharmacogenomics can be used to identify specific groups (rather than individuals), a recent publication introduces the term stratified medicine. Pharmacogenomics is a rapidly advancing field in medical science, and the terminology is still being established. When contemplating the integration of pharmacogenomics into global drug development initiatives, it is crucial to comprehend the terminology employed in scientific literature and regulatory documents. It has been observed in several instances that personalized medicine has been gaining popularity and increasing awareness among the general public, thanks to extensive news and media coverage.

The basis of pharmacogenomics

The initial pharmacogenomic-type medication was developed to address the treatment of alkaptonuria, a metabolic disorder. In 1902, studies proposed a genetic basis as the potential cause [3]. During World War II, it was discovered that African-American soldiers were more likely to experience hemolysis as a side effect of antimalarial treatment, prompting the identification of a specific enzyme as the genetic factor responsible. Pharmacogenetics is the primary area of study in genes, which plays a significant role in the understanding of. 'many genomes, one drug,' suggesting that patient variability is essential to achieve the desired product In contrast to pharmacogenomics, the concept of pharmacogenetics revolves around tailoring drug compounds to match the specific genome, resulting in the development of'many drugs, one genome [5]'. Both tailor to an individual's drug metabolism and response to minimize side effects, but the concept of pharmacogenomics is broader in its application to the pharmaceutical industry as a tool for selecting compounds.

Short term benefits

Of the 3 billion prescriptions per year, an estimated 3 million are incorrect or ineffective, resulting in over 100,000 deaths per year from adverse drug responses (adrs) in united states [8,9], ranking this between the fourth- and the sixth-leading cause of death. Since drugs are currently prescribed to treat a specific condition, a drug could be prescribed to anyone with that condition without knowing how they will respond to it. Indeed, a blockbuster drug – a commercially successful drug for the overall population – is only efficacious in 4060% of the general

population [10].The authors of this study have shown that the efficacy of a drug is not only dependent on the drug itself, but also on the patient's genetic makeup.

Long term benebits

One expected outcome of pharmacogenomics is a more efficient healthcare system. By combining a patient's clinical history with their genetic traits, physicians can offer more precise recommendations. When patients have confidence in the healthcare system, their attitudes and behaviors towards their health may become more positive. Currently, due to the large number of ineffective prescriptions, half of all patients stop taking their medications for chronic

Implications of genetic testing

The first category of genetic testing aims to pinpoint how an individual processes drugs, covering everything from absorption and distribution to metabolism and excretion. The second category concentrates on aligning individuals with specific drug compounds to enhance their effectiveness. Lastly, genetic testing can identify individuals who have a heightened risk for particular health conditions.

Through genetic testing, individuals can gain predictive insights into their health and susceptibility to various diseases or conditions. By analyzing specific segments of their genetic code associated with particular predispositions, they can evaluate their chances of developing certain illnesses. However, the response to this information can either motivate or deter changes in behavior, even when the outcomes are independent of environmental factors. This raises concerns about the manner in which test results are communicated. If results are presented without proper context, they may inadvertently exaggerate the perceived risk of an individual's predisposition, leading to an inflated interpretation and subsequent reaction. Conversely, if an individual anticipates certain outcomes based on family medical history yet does not receive supporting evidence from genetic testing, they may feel a sense of relief, but more commonly, they might be inclined to doubt the results.

Impact on the Pharmaceutical Industry

The conventional blockbuster business model optimizes its production pipeline to yield a select number of billion-dollar products annually. By concentrating on a limited range of high-revenue products, pharmaceutical companies are encouraged to create medications for the wider public, particularly those intended for long-term use. The accompanying figure illustrates the typical development process and its timeline.

Initially, around 10,000 compounds are gradually streamlined through the drug discovery and development process to arrive at a single, robust compound that will be the patented active ingredient in the medication. Advances in technology, such as high-throughput screening and microarrays, have accelerated the ability to swiftly isolate and identify potential drug candidates. The preclinical phase poses the greatest limitation in the overall timeline, as thorough analysis of toxicity and safety is required in laboratory tests and animal studies to ensure that only those candidates deemed safe can progress to human trials.

During Phase 2 clinical trials, a targeted group of volunteers, excluding the elderly, young subjects, and individuals with other illnesses, is selected to evaluate the drug's efficacy. By utilizing pharmacogenetics, insights into the correlation between efficacy, safety, and biomarkers can uncover vital information. This information may facilitate the narrowing of the population to those most likely to respond positively or allow adjustments to the active ingredient of the compound.

Phase 3 clinical trials represent the most extensive and thorough phase. Thankfully, through the application of pharmacogenomics, the initial participant group can be significantly reduced after non-responders are identified. Consequently, after the drug reaches the market, patients experiencing severe side effects can be monitored to explore the genetic factors underlying these reactions.

Challenges for PGx analysis during clinical development

Genetic analyses utilizing clinical trial data can serve as a vital foundation for informed decision-making throughout the clinical development lifecycle, potentially unlocking significant clinical and commercial opportunities related to patient stratification and therapeutic value propositions (Nelson et al. 2016). However,

several challenges and limitations hinder the execution of genetic analyses during clinical development, such as small sample sizes, insufficient global representation, and challenges in validating results.

Primarily, many clinical studies are not specifically designed around a genetic or pharmacogenomic (PGx) hypothesis as their main objective. Instead, these studies focus on therapeutic hypotheses and are structured to identify differences in safety and efficacy, relegating genetic or PGx objectives to tertiary or exploratory status. Phase I trials often lack the statistical power needed for candidate variant analyses unless data from multiple studies are combined (Guo et al. 2019; Kobie et al. 2019). Although phase II and phase III trials involve larger groups of participants, they can still be underpowered for conducting genome-wide association studies.

Another significant issue is the lack of diversity among populations participating in clinical trials. A majority of trial participants are of European descent (FDA 2017). This skew is not exclusive to genetic analyses within clinical studies but reflects a broader limitation in current genetic research (Popejoy and Fullerton 2016). Consequently, insufficient representation of global genetic diversity in PGx studies can result in overlooked signals that are crucial in clinical settings. Many clinically relevant PGx biomarkers are found predominantly or with much higher frequencies in non-European populations. For instance, HLA-B*15:02, associated with cutaneous adverse reactions to carbamazepine or oxcarbazepine, is primarily present in certain East Asian and South Asian groups (Phillips et al. 2018). Similarly, the CYP2C19 poor metabolizer phenotype, linked to varying risks of adverse effects or efficacy for a range of drugs, appears at significantly higher frequencies in Asian populations (Scott et al. 2012). The absence of diverse populations in studies means these important associations may go undetected. Furthermore, assessing whether findings from a genetic association study based on predominantly European participants are applicable to other (non-European) populations becomes difficult when subject availability is limited.

Lastly, for new chemical entities and drugs with innovative mechanisms, data generated from early clinical development programs are often the first and only available, complicating the confirmation or refutation of new genetic discoveries until subsequent clinical trials are completed. Nonetheless, variations in clinical trial designs, population diversity, and the lack of statistical power for replication may also complicate the interpretation of PGx findings from later clinical studies (Hopewell et al. 2019; Shen et al. 2020). This uncertainty surrounding the clinical utility of genetic analyses during drug development can deter the initiation of exploratory investigations, as the risk associated with generating uninterpretable or unconfirmable exploratory findings may outweigh any potential benefits.

Emerging scientific opportunities: large genomic databases for drug development

Pharmaceutical companies are increasingly leveraging extensive genomic datasets associated with patient health and medical information through partnerships, collaborations, or acquisitions. Table 1 presents several examples of these consortiums and partnerships. These databases serve as a crucial resource for comprehensive genomic research pertinent to drug development. The primary aim of these research initiatives is to pinpoint genes linked to diseases and discover new drug targets (Dewey et al. 2016; Szustakowski et al. 2020; Van Hout et al. 2020). Moreover, large-scale genomic databases offer an unparalleled wealth of information regarding both the safety and effectiveness of current clinical development programs as well as drugs already on the market (Diogo et al. 2018; McInnes et al. 2020). Drug targets supported by genetic evidence demonstrate higher success rates in the drug development process (Nelson et al. 2015). Various types of genetic variations can yield valuable insights for potential drug targets, with particular attention on loss of function (LOF) variants, which have gained considerable interest in drug development. These variants, when linked to reduced disease risk, may simulate the effects of therapeutic antagonists (e.g., PCSK9) (Cohen et al. 2006). Furthermore, the profiling of drug targets through phenome-wide association studies (PheWAS) within these extensive databases can unveil novel indications, related health issues, or even safety concerns (Diogo et al. 2018; Jerome et al. 2020). Additionally, the insights derived from these large databases can bolster evidence for variants identified in pharmacogenomic (PGx) analyses of ongoing clinical trials for drugs that are still in the development phase. Ultimately, distinct genetic subpopulations of patients may be identified to support targeted precision medicine clinical development initiatives or to facilitate follow-up studies aimed at more detailed patient phenotyping.

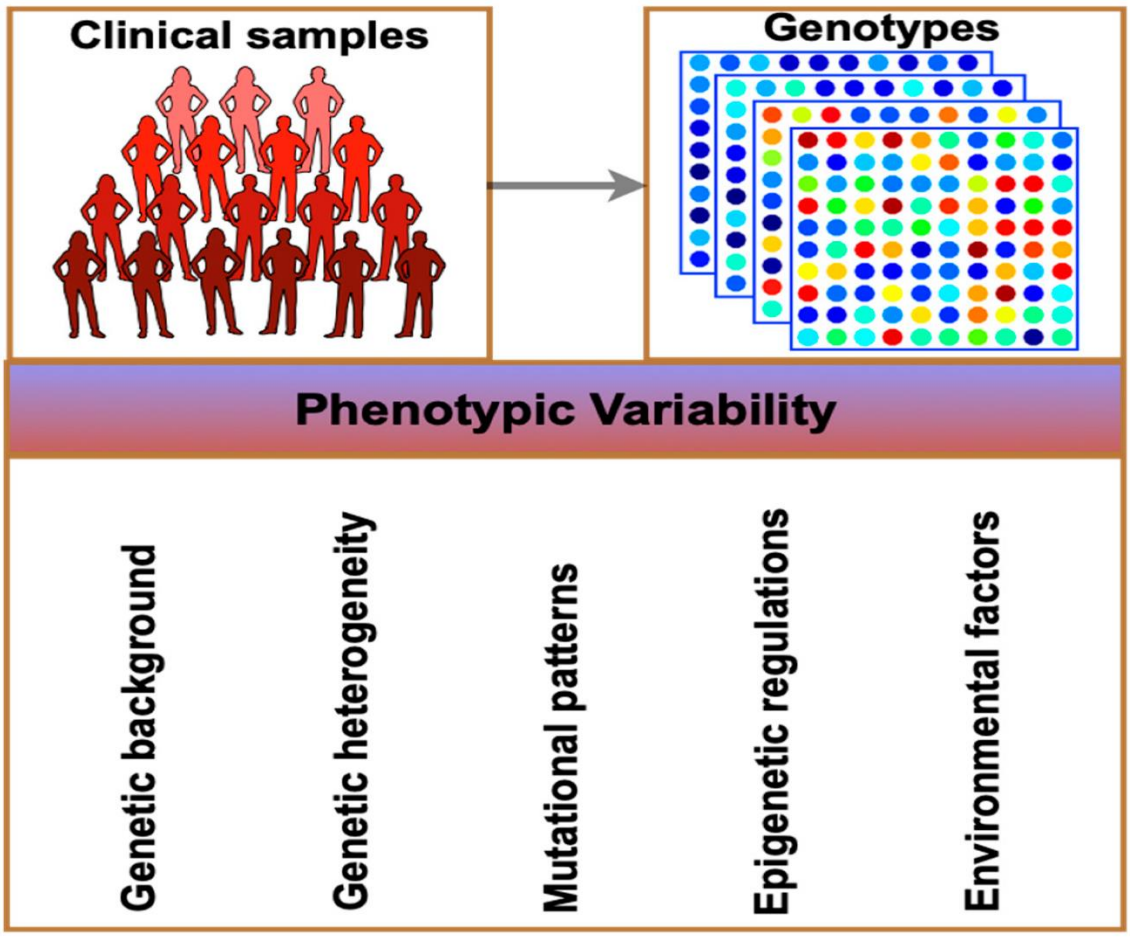
Emerging scientific opportunities: sequencing PGx clinical trial subjects

Over the past few years, the decline in costs associated with high-throughput sequencing and genotyping has enabled companies to routinely conduct extensive genomic characterization of participants in clinical trials. A 2017 survey of I-PWG members revealed that 79% of responding companies had implemented next-generation

sequencing (NGS) technologies in at least one internal pharmacogenomics (PGx) study, with more than one-third extensively utilizing these technologies. Specifically, 53% of companies reported employing NGS for whole-genome sequencing and 71% for whole-exome sequencing of clinical trial participants. Although NGS technologies were predominantly utilized in oncology studies, companies also noted their application in various other therapeutic areas outside of oncology for PGx research, including cardiovascular, neuroscience, immunology, and rare diseases. Utilizing NGS for clinical trial samples facilitates a more thorough genomic assessment of participants and potentially broadens the scope of PGx analyses by encompassing both common and rare genetic variations (Schwarz et al., 2019).

Genetic Factors Influencing Individual Drug Response Variability

The extensive diversity in pharmacological responses and toxic effects, along with phenotypic differences, hampers the use of certain medications in clinical practice (see Figure 2). Fewer than 70% of patients achieve a satisfactory response with some of the most advanced drugs currently available, and many experience adverse effects, resulting in a suboptimal risk/benefit ratio for numerous patients. To comprehend this variability, one must delve into the realms of pharmacokinetics (PK) and pharmacodynamics (PD), which offer quantitative analyses of drug exposure and its effects. PD primarily addresses drug targets—such as receptors and enzymes—along with subsequent signaling pathways and pharmacological outcomes, while PK emphasizes the processes of absorption, distribution, metabolism, and excretion (ADME). Numerous polymorphic genes play pivotal roles in the PK-PD relationship [46,47,48]. As ADME influences the level of medication exposure, monitoring these levels can provide phenotypic indicators beneficial for personalized therapy [49]. Previously, high-throughput technologies have facilitated PK screenings to identify predictive biomarkers for toxicity or efficacy in cancer treatments. The clinical integration of these biomarkers could pave the way for tailored therapies based on an individual's genetic profile. The use of pharmacogenomic technologies and the implementation of pharmacogenetic screening may enhance patient safety by identifying drug metabolism-related biomarkers for customized treatment approaches. Promising findings have emerged from pharmacogenetic research in pediatric populations, despite most pharmacogenomic studies focusing on adults. A meta-analysis indicates that polymorphic drug-metabolizing enzymes are associated with serious adverse pharmacological effects [17,50,51].



Protein therapies, which include various biologics like therapeutic enzyme replacements, fusion proteins, and antibodies, have revolutionized the treatment landscape for a range of conditions, including cancer, autoimmune disorders, inflammatory diseases, respiratory issues, vascular problems, and neurological disorders. While protein therapies are often the focus of in vivo studies on pharmacokinetics, pharmacodynamics, and efficacy, insufficient attention has been given to identifying the key factors that influence the ADME properties of these agents. Comprehensive characterization and thorough investigation of their ADME characteristics are crucial to support drug research and development efforts aimed at creating safer and more effective biotherapeutics, thereby offering a strategy to mitigate the risk of adverse outcomes utilizing genetic information.

Future of Genotypes in Drug Therapeutics

If a strong and frequent genetic factor is present, it may be advisable to conduct prospective genotyping, especially if acquiring optimal pharmacological treatment could lead to severe consequences. In many instances, identifying the genetic factors responsible for differing drug responses could significantly reduce the risk of serious side effects. Evidence from human genetics supports the therapeutic hypothesis, increasing the likelihood that a medication will succeed in clinical trials. Both common and rare disease genetics yield numerous alleles with varying effect sizes, which can serve as indicators of a drug's efficacy for a specific condition. Recent advancements in large-scale population studies and whole genome sequencing have generated extensive genetic information about humans, aiding in the selection of therapeutic targets. As the range of phenotypes studied expands and additional alleles from diverse populations are identified, these methods are poised to have a greater influence on various stages of drug development. However, prospective genotyping in a therapeutic context raises practical, legal, and financial challenges, prompting mixed opinions on its application. Alternatively, careful monitoring of white blood cell counts may suffice in preventing significant toxicity. It is evident that ethical, legal, economic, and medical considerations must be weighed when implementing potential genotyping in a clinical setting.

Drug Response

Clinical drug response, a complex phenotype, arises from the interplay of various factors, including genetic, clinical, environmental, and demographic elements (Figure 2). This complexity leads to significant variability in how individuals respond to medications, affecting both the effectiveness and toxicity of treatments, ultimately resulting in inefficient use of limited healthcare resources. Pharmacogenomics seeks to optimize therapeutic efficacy and minimize adverse drug reactions through genotype-informed prescribing and monitoring guidelines, focusing on the genetic factors that contribute to variations in drug response. Established pharmacogenomic associations can be found for several approved cardiovascular drugs, such as simvastatin (SLCO1B1), warfarin (VKORC1, CYP2C9, CYP4F2), and clopidogrel (CYP2C19) [57,58].

Interindividual variability in drug response can be defined in two ways: the necessity for different doses to achieve a specific level of effect in each patient, or the variability in effect strength among individuals taking the same dosage of a medication. Drug reactions can be categorized into four types: toxic effects, lack of effect or therapeutic failure, adverse reactions, and the intended therapeutic effect (efficacy). Medication dosage significantly impacts side effects and therapeutic failures. In the field of precision oncology, predicting drug responses based on the genetic profiles of cancers is vital. Most existing drug response prediction models have been developed using drug screening data from immortalized cancer cell lines, which frequently exhibit different genetic characteristics compared to patient tumors. Patient-derived organoids (PDOs) are increasingly being used as a platform to accurately replicate patient-specific cancers

The conventional approach of using single-agent therapies that target a single receptor is no longer regarded as the most effective strategy for treating complex diseases such as cancer and HIV/AIDS. However, when multiple medications are administered simultaneously, the risk of drug-drug interactions increases, potentially leading to unexpected and difficult-to-identify adverse effects [9]. For instance, if a patient has a poor metabolism for CYP2D6 and takes medication A alongside another drug that inhibits CYP2C9, the metabolism of the first medication, which relies on both CYP2D6 and CYP2C9, is significantly reduced. Ritonavir is employed as an antiviral "booster" in conjunction with up to three antiviral agents during HIV therapy. Depending on the mechanism, ritonavir serves as a potent inhibitor of membrane transporters such as CYP3A4 and Pgp (MDR1), allowing for reduced dosages of other antivirals that are also processed by CYP3A4 and transported by Pgp, although this can lead to unpredictable dosing. Moreover, to mitigate the lipodystrophic side effects associated with antivirals, many patients are co-prescribed statins, antidepressants, and antibiotics [53]. Severe side effects

often occur with high frequency and intensity, likely influenced by polymorphisms in genes related to ADME (absorption, distribution, metabolism, and excretion). The “one gene, one drug” paradigm may complicate establishing causal relationships, as effects tend to be distributed throughout a network of interactions. Thus, a systems biology approach that integrates overall adverse effects with functional variations across multiple genes is essential. We propose a medical informatics strategy that assesses all side effects, especially those concerning large patient populations, in relation to the most prevalent pharmacogenetic markers.

Genetic Factors Influencing Phenotypic Diversity

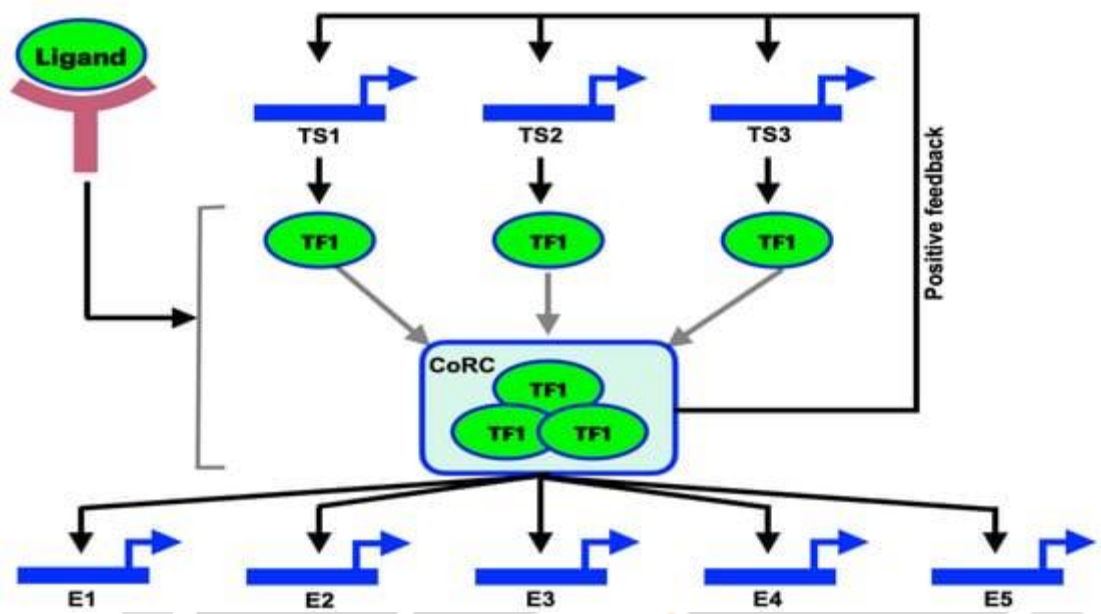
Changes in DNA sequences can significantly influence mRNA stability and processing, protein structure and function, and gene expression regulation. Comprehensive research on genetic diversity has revealed that polymorphisms affecting cis-regulatory elements are far more prevalent than those that modify the fundamental structure and functionality of proteins. While the majority of these polymorphisms remain unidentified, it is predicted that nearly all genes harbor one or more polymorphisms at various cis-regulatory locations throughout the gene locus. Moreover, genetic variants can also affect alternative splicing and mRNA stability during the mRNA processing stage. Current estimates suggest that 35–59% of human genes undergo alternative splicing. Although many polymorphisms have been identified to influence splicing—such as mutations in CYP2D6—only a few, like a synonymous SNP in the dopamine DRD2 receptor, have been shown to impact mRNA stability. However, findings from computational studies suggest that most SNPs could influence mRNA folding, thereby affecting mRNA stability, processing, or translation.

Previous studies and evaluations indicate that variations in phenotype can often be attributed to cis-acting polymorphisms that modify mRNA functions. This typically leads to an imbalance in the expression levels of the two alleles involved in mRNA production (allelic expression). To detect such imbalances, a method that employs PCR amplification of genomic DNA alongside mRNA (as cDNA) from a transcribed gene region featuring a shared marker SNP can be utilized. The subsequent step involves analyzing the allelic ratios present in both DNA and mRNA. Each allele operates under its own regulatory system to mitigate transacting effects. A considerable number of marker SNPs can be employed to observe polymorphic alterations in splicing events. Due to the different regulation of transcription and mRNA processing in target tissues, tests need to be conducted within those specific environments. In situations where trans-acting mechanisms (like transcription factors) contribute to variability in mRNA levels, it is critical to identify the upstream cis-acting polymorphisms within the signaling pathways. Despite its potential as a valuable tool for identifying cis-acting factors, the low reproducibility of allelic expression imbalance analysis may limit its application. Variations in expression patterns of significant genes can lead to diseases or affect treatment outcomes. Additionally, epigenetic modifications have been shown to cause allelic mRNA imbalances. Analyzing the ratio of allele DNA to mRNA is one effective method for identifying interindividual differences in mRNA processing and gene expression. This approach provides quantitative traits that can be utilized to pinpoint cis-acting influences and is particularly sensitive to these various processes.

Epigenetic Effects and Regulation of Gene Expression at the mRNA and Protein Level

Animal cells exist in a wide range of forms and serve as the fundamental building blocks of all multicellular organisms. Although methods for categorizing these cells are often unclear, significant progress has been achieved in the identification of various cell types. We present an evolutionary perspective on cell types, facilitating their differentiation and comparison both within and among species. The "core regulatory complex" (CoRC) of transcription factors has evolved to identify newly emerged sister cell types, promote their autonomous development, and regulate apomeres—traits unique to specific cell types. These changes are crucial for accurately defining cell types. We explore the differences between developmental and evolutionary lineages and outline a proposed research agenda for the future. Even without genomic DNA polymorphisms, modified gene expression can be inherited across generations through mechanisms such as chromatin remodeling and imprinting, as well as during divisions of somatic cells. In this context, we include a figure from earlier research [1] illustrating a straightforward regulatory mechanism for cell-type identity, highlighting the various levels at which regulation occurs (Figure 3). The key processes behind these heritable characteristics include the methylation of CpG islands and histone modifications through acetylation and methylation. Additionally, global methylation is necessary for X chromosome inactivation, mediated by the Xist transcript, which explains differences in gene dosage between males and females. The frequent bias in X-inactivation leads to uneven allele expression. Recent studies indicate

that epigenetic modifications broadly influence diseases and may offer potential therapeutic advantages [68,69]. Prolonged manic and depressive episodes in bipolar disorder may be triggered by metastable, reversible epigenetic changes affecting gene regulation. Treatments such as decitabine and HDAC inhibitors aim to induce the expression of tumor suppressor genes by enhancing histone acetylation and reversing CpG methylations. This is because the same epigenetic mechanisms that suppress tumor suppressor genes also appear to impact cancer. Conversely, the effectiveness of cancer treatments like cisplatin and BCNU is enhanced by the methylation of the MGMT promoter, which encodes a DNA repair enzyme. While it is clear that epigenetic alterations influence disease and treatment outcomes, there remains insufficient knowledge to effectively apply this understanding in a personalized medical context in the future.



illustrates the regulatory signature for cell-type identity [1]. This model aids in distinguishing various cell types. A select group of terminal selector genes (TS1 to TS3) generates transcription factors (TF1 to TF3), which undergo modifications when ligands bind to them, leading to the formation of a core regulatory complex (CoRC) through the activation of signaling pathways. The CoRC, as a molecular agent, is crucial for sustaining its own expression while also regulating downstream effector genes (E1 to E5). In essence, terminal selector transcription factors collaborate to create the CoRC, which governs the expression of genes specific to a particular cell type, thereby supporting the evolutionary distinctiveness of that cell type.

Recent research on small regulatory RNAs has highlighted the intricate nature of gene regulation and translation. This includes studies on antisense transcripts derived from the opposite DNA strand of several genes, mechanisms involving siRNA, and the emerging field of microRNAs. With nearly 1,000 microRNAs identified in the human genome—each targeting multiple genes—these molecules are expected to play a pivotal role in both disease mechanisms and therapeutic responses. In particular, microRNAs may significantly influence chemosensitivity and resistance in response to chemotherapy.

Ethical Concerns:

Numerous ethical concerns arise, primarily due to the potential emergence of "designer drugs," which may lead to a situation where poorer and disadvantaged individuals and nations struggle to access high-quality healthcare. This situation threatens to exacerbate the existing gap between the wealthy and the impoverished. If major pharmaceutical companies do not embrace the concept of pharmacogenomics, this disparity could become a significant issue. Another critical ethical dilemma involves the use of genetically modified animals in the production of human medications, a practice known as "pharming." This approach may involve domestic animals at an unprecedented scale in the medical field, raising serious ethical questions about their treatment. This concern is particularly pressing given the ongoing debate regarding animal testing.

Conclusions and Future Perspectives

The pharmaceutical industry stands to benefit greatly from pharmacogenomics, which represents a notable progression in the history of medicine. Its primary objectives include identifying new targets for groundbreaking drugs, minimizing adverse drug reactions, enhancing treatment efficacy, and utilizing pharmacogenetic profiles to predict disease risk and response to therapy. Historically, drug development typically addressed the general population rather than focusing on individual patients. However, pharmacogenomics shifts this paradigm by refining therapeutic approaches, boosting drug effectiveness, and mitigating side effects. Unlike traditional methods that emphasize the disease's observable traits, known as the phenotype, pharmacogenomic therapy delves into the genetic blueprint, or genotype. Ultimately, pharmacogenomic research is expected to be integrated into drug development processes, leading to reduced costs, lower failure rates, and improved safety in clinical trials. This integration promises to preserve many potential drugs that might otherwise be dismissed due to their impact on study outliers.

Despite its future promise, the practical application of pharmacogenomics remains years away. Progress is being made in understanding how patients respond to medications, but several hurdles must be overcome before pharmacogenomics can be effectively implemented in therapeutic contexts. The ways in which drugs and combinations interact with the body involve numerous pathways, and pharmacological interactions can produce unexpected effects linked to polymorphic genes. A comprehensive systems analysis in medical informatics is required to compile all relevant information for an in-depth genetic investigation of pharmacological responses. A quantitative grasp of how genetic factors influence the target phenotype is crucial. Alongside molecular genetic analysis of polymorphisms that affect the fundamental structure of proteins, we advocate for the systematic assessment of allelic expression imbalances to quantitatively evaluate cis-acting elements involved in transcription and mRNA processing.

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