

Genetic Polymorphisms in Pharmaceuticals and Chemotherapy

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Abstract

The study of genetic polymorphisms has significantly advanced the field of personalized medicine. Polymorphism of genes influence the efficacy of drugs used for treating medical conditions such as depression, cardiac diseases, thromboembolic disorders, oncological diseases, etc. The study of genetic polymorphism is beneficial for drug safety as well as for assessing therapeutic outcomes. Understanding and detecting genetic polymorphisms early on in patients can be useful in selecting the correct chemotherapeutic agent and appropriate dosage for a patient. Knowing the genetic profile of a patient and the interindividual response to various drugs significantly influences the proper selection of medication - a key step towards personalized medicine. Polymorphisms also make patients susceptible to certain cancers and identification of these polymorphisms early can be useful for a personalized treatment plan. The Genome-Wide Association Studies (GWAS) project where millions of genetic variants in the genomes of many individuals are studied to identify connections between what is present on the gene and the phenotype of the patient has enhanced the prospect of personalized medicine. GWAS has been used to identify hundreds of diseases associated to genetic polymorphisms. Individual pharmacokinetic profiles of patients to drugs enable the development of early surveillance protocols to prophylactically prevent patients from having adverse reactions. Furthermore, patient-derived cellular organoids are another advancement that allows researchers to screen for polymorphisms of the patient for adverse reactions from chemotherapy and will allow for the development of new medications that are specific to the profile of the patient's tumor. These advances have led to significant progress towards personalized medicine. The functional consequences of genetic polymorphism on cancer drugs and treatment are studied here.

Keywords: Genetic polymorphisms; Personalized medicine; Pharmacokinetics; Cancer; Chemotherapy

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Introduction

The origin of genetics, the study of genes, began in 1866 with Gregor Mendel and his examination of the hereditary behavior of garden peas. Hershey and Chase later discovered that genes are made of DNA and Watson and Crick eventually discovered that DNA is responsible for forming proteins, which are the basis of all traits [1]. It was quickly realized that changes in the DNA had effects on the individual's physiology which led to a rush to determine the entire DNA sequence of the human genome. This project, the Human Genome project yielded that between humans, 99.5% of the human genome is conserved and there is variation from individual to individual in the remaining portion of the genome [2, 3]. If these variants are present with a greater than 1% frequency in the population, they are considered genetic polymorphisms [3]. If the variants are less than 1%, they are genetic mutations. There are different types of polymorphisms that differ based on the length, location, and number of repetitions.

The area of variation can be a change in one single nucleotide, also known as a single nucleotide polymorphism (SNP) or it can involve longer stretches. Other forms of genetic polymorphisms include tandem repeat polymorphisms, short tandem repeats, and copy-number polymorphisms. Tandem repeat polymorphisms are sequences of DNA that are repeated multiple times within the non-coding portions of sequences. Short tandem repeats are units of 1 - 6 repeated base pairs that appear in a repeated fashion within DNA sequences [4]. Copy-number polymorphisms are large portions of a genome that vary in copy number from person to person as a result of duplication or deletion events [5]. As a whole, genetic polymorphisms are responsible for the wide genetic array that is present within the population.

Genetic polymorphisms can occur for a variety of reasons. Sometimes, these genetic polymorphisms can be a result of chance or at times, they may be a result of external agents such as radiation [6]. Regardless of the source, genetic polymorphisms are significant because they can serve as markers of disease and sometimes, can also provide an explanation for variations in response of patients to different medications [7]. Polymorphisms are important in the clinical setting because they may alter the key enzymes that control metabolism, transport, and uptake of therapeutic treatments. The study of polymorphisms and their impact on drugs present an opportunity to create individualized therapies based on genetic profile, a step towards personalized medicine. The impact of polymorphisms on pharmaceuticals and chemotherapy is discussed here.

Hypothesis Behind Different Responses to Drugs due to Genetic Polymorphisms

Interindividual variations in response to drug treatment often present a challenge in the treatment process. It is estimated that genome of a typical individual consists of 14 million SNPs. Every SNP presents a persistent source of variation in a patient's response to drugs. It is hypothesized that polymorphisms affect the pharmacokinetics and pharmacodynamics of drugs. Pharmacokinetics refers to the rate of movement of the drug throughout the body and focuses on drug absorption, distribution and metabolism. Pharmacodynamics refers to how well receptors, ion channels and other various targets respond to drugs. Both pharmacokinetics and pharmacodynamics can influence the range of a drug's effect. Single base variations in the genes coding for metabolizing enzymes, drug transporters as well as target sites can affect how a drug responds in the patient's body. A study that examined the effect of drug response between individuals determined that genetic factors contribute 20-95% of variability in drug response [8]. Other polymorphisms that could lead to a variation in drug response include mutations in the gene coding region which could lead to a reduction or loss of function of proteins responsible for the functionality of the medication. The varied response to medications that patients experience has the potential to cause severe damage or even death. As a result, it is imperative to understand and develop effective and cheap genetic sequencing techniques. The impact of genetic polymorphisms on commonplace medications is significant.

Pharmacological Consequences of Genetic Polymorphisms

Any foreign substance taken into the body - termed xenobiotics - must be metabolized and excreted and medications are no exception. All xenobiotics are metabolized in a three-step process: phase 1 is modification, phase 2 is conjugation and phase 3 is excretion [9]. Polymorphisms can occur in genes that control a majority of these stages of the metabolization process. The variation in genes can lead to an altered response to xenobiotics.

Phase 1 of the metabolism process is known as the modification phase. This phase consists of changing the structure of a drug, typically through oxidation with the goal of making the medication polar enough to excrete. The modification process does not always make xenobiotics inert [10]. The most important enzymes in the phase 1 metabolism process are the cytochrome p450 enzymes (CYP450). The CYP450 enzymes are integral for the metabolism of many drugs such as opioids as well as the activation of prodrugs [10, 11]. There have been over 2,000 mutations identified in the CYP family and many of those are known causes of variable drug response and metabolism [11]. The first genetic polymorphism made known in the CYP family was found in the CYP2D6 enzyme. This polymorphism was discovered 30 years ago when a small group of patients who were administered the antihypertensive drug debrisoquine had a severe drop in blood pressure

that led to the observation that there were high levels of debrisoquine in the plasma of these patients. It is now known that the CYP2D6 enzyme is responsible for the metabolism of 25% of drugs including antidepressants, beta-blockers, opioids, and antiarrhythmic agents [12, 13]. Individuals within the population have different allelic variants of CYP2D6 and their variants determine their metabolism status. The population is divided into "extensive metabolizers", "intermediate metabolizers", "poor metabolizers", and "ultrarapid metabolizers". The range in polymorphism leads to up to a 10-fold difference in the required dose of medicine necessary in order to achieve identical plasma concentrations in individuals. Individuals who have two non-functional alleles have the poor metabolizer phenotype while those with two normal alleles are labelled as extensive metabolizers. Poor metabolizers are unable to break down the drug into an excretable form, and as a result, have a higher concentration of the medication in their plasma. This results in greater and more frequent adverse drug reactions. On the other hand, extensive and ultra-rapid metabolizers break down medications at a very fast rate. This causes low plasma levels of the medication and thus higher dosage of medication administration is necessary for efficacy. However, higher amounts of certain medications can lead to toxicity and sometimes, fatality [12]. The medication metoprolol, a frequently prescribed cardiovascular medication, is one of the many medications that are metabolized by CYP2D6. It was shown that individuals with poor metabolizer status or ultra-rapid metabolizer status are susceptible to side effects or therapeutic failure [14]. Another polymorphism within the CYP450 family is in the CYP2C family in which there is the CYP2C9 variant. It was shown that patients with this variant after administration of warfarin had increased international normalized ratio (INR) and warfarin content in their plasma [12]. The variable response that patients can have based on their modification status underscores the importance physicians must take when dosing patients.

The next stage of the metabolism process is the conjugation process, and this involves the addition of various chemical groups in order to facilitate the inactivation of a xenobiotic. Some forms of conjugation include glucuronidation, sulphation and acetylation. One of the first major polymorphisms associated with drug conjugation is variations in the N-acetyltransferase (NAT). NAT is an enzyme that is responsible for catalyzing the addition of acetyl groups onto xenobiotics in order to excrete them. NAT is controlled by the *NAT-1* or the *NAT-2* gene. The *NAT-2* gene has two variants, *NAT2-A* and *NAT2-B* gene which are polymorphisms. The polymorphisms can produce two groups of patients - one variant produces fast acetylators while the other variant produces slow acetylators. The rate of acetylation can affect the amount of drug concentration that remains in the plasma and can produce many different clinical outcomes. Slow acetylators can have more side effects because they remain in the plasma longer while fast acetylators may have less of a clinical response because they are excreted more quickly. Some slow acetylators include dapsone and procainamide and individuals with this variation can have severe symptoms such as red cell toxicity [12, 15]. Overall, there are many examples of polymorphisms in drug metabolism that affect the way that therapeutics interact in a

patient's body. Polymorphisms can also affect the effectiveness of chemotherapeutic agents used for cancer treatment.

Role of Polymorphisms in Cancer Treatment

Cancer continues to be one of the leading causes of deaths worldwide and as such has warranted an increase in research regarding treatment [16]. Progress in oncological treatments has continued and become more individualized to address the differences in polymorphisms among patients. Understanding and detecting polymorphisms early on in patients can be instrumental in selecting the correct chemotherapeutic agent for a patient. As discussed earlier, there are a multitude of polymorphisms in the enzymes that regulate drug metabolism, specifically in the CYP enzymes. More specifically, the CYP2 family of enzymes are important for the metabolism of cancer drugs. Tegafur is a widely used chemotherapeutic drug for treating multiple types of cancers in stomach, breast, pancreas, bowel, etc. CYP2A6 enzymes are necessary to convert the prodrug Tegafur into 5-fluorouracil (5-FU) which is effective against numerous tumors. Patients with the CYP2A6*4 allele had decreased conversion of Tegafur into 5-FU resulting in less therapeutic effects to the patient. Patients with the CYP2A6*1B variant was associated with increased conversion of Tegafur into 5-FU. Knowing whether a patient has these mutations is integral to proper selection of medication [9, 17].

One of the most well-known examples of a cancer treatment affected by genetic polymorphisms is in the *TPMT* gene. The *TPMT* gene catalyzes the methylation of thiopurines including 6-mercaptopurine and 6-thiopurine. The 6-mercaptopurine is a very commonly used chemotherapeutic agent used in the treatment of acute lymphoblastic leukemia as well as other cancers. Studies indicated that *TPMT**3A and *TPMT**3C alleles reduce the stability and activity of the *TPMT* enzyme and people with these genetic compositions are *TPMT*-deficient. Approximately 1/300 have *TPMT* deficiency and if those patients are treated with the standard dosage of thiopurine chemo, they end up accumulating excessive medication in their blood leading to hematopoietic toxicity. As a result, it is imperative to perform a molecular assay to determine if patients have this polymorphism before administration of thiopurines [9, 18].

Another well-known genetic polymorphism that affects cancer treatment is in the *UGT1A1* gene. UDP-glucuronosyltransferases family of metabolizing enzymes are responsible for glucuronidation which converts lipid soluble metabolites into water soluble metabolites so that the body can excrete them. The *UGT1A1* gene in enzyme is responsible for detoxifying metabolites. Patients with genetic polymorphism of *UGT1A1*, known as the *UGT1A1**28 variant, have an additional TA repeat in the promoter region of the gene which leads to reduced functionality and reduced production of the UDP-glucuronosyltransferase enzyme. As a result, when they are administered certain chemotherapeutic agents, it leads to a toxic buildup. One of the most well-known examples of this is with the administration of irinotecan. Irinotecan is a commonly used chemotherapeutic agent that is a topoisomerase one inhibitor that is typically used to treat advanced colorectal

cancer. When patients have the *UGT1A1**28 variant, there is reduced excretion of irinotecan and higher levels in the blood leading to severe neutropenia and diarrhea. It is important to be aware of the patient's genetic history as the dosage of irinotecan given to a patient is dependent on their *UGT1A1* genotype [18, 19].

Variation in the methylation of O(6)-methylguanine-DNA-methyltransferase or *MGMT* protein is another important polymorphism that has an effect on the efficacy of chemotherapy. The *MGMT* enzyme functions by removing alkylating groups from guanines and preventing mutagenesis of cells from occurring. The enzyme also prevents the effects of alkylating chemotherapeutic agents such as carmustine. It has been shown that an increased presence of non-functional *MGMT* is related to a higher likelihood of carcinogenesis. However, the rate of success that patients have with usage of alkylating chemotherapy is also associated with non-functional *MGMT* [20, 21]. The most common mechanism for downregulated *MGMT* is hypermethylation and one of the most well-known cancers that display this process are gliomas. The expression of *MGMT* can also be affected by SNPs in the promoter region of the gene. It is suspected that a combination of hypermethylation and SNPs are the cause of varied expression of *MGMT*. Specifically, there are polymorphisms such as rs16906252:C>T that have been linked to *MGMT* methylation in many forms of cancer including glioblastoma, mesothelioma and colorectal cancer [20]. The copy number loss of chromosome 10q is also associated with lack of *MGMT* and thus higher incidence of glioblastoma [22]. The significance of knowing if a patient with these cancers have downregulated *MGMT* is that alkylating chemotherapeutic agents such as carmustine and temozolomide are more effective treatments. As a result of *MGMT* functioning to antagonize the effects of alkylating agents, cancers with that mutation allow for success with alkylating chemo agents [22, 23].

Polymorphism of the glutathione S-transferase (*GST*) enzyme is another example. The *GST* enzymes catalyze the glutathione-dependent detoxification of several chemotherapeutic drugs or their metabolites. Polymorphisms of *GST* alter the metabolism of chemotherapeutic drugs and modify the effectiveness of therapy, as suggested by reports that *GST* polymorphisms predict differences in outcomes of treatment for cancers including breast cancer, leukemias and colorectal cancer. Some of the known polymorphisms and their impact on cancer treatment are listed in Table 1 [9, 14-17, 23, 24].

Genetic polymorphisms can also occur in drug transporters, and this affects the ability of the drugs to be excreted from the body. One major example of a drug transporter that is affected by genetic polymorphisms is the P-glycoprotein (P-gp). P-gp is a member of the ABC family of transporters and is responsible for pumping foreign substances such as xenobiotics out of the cell. The P-gp is coded for by *MDR-1* and variations in this gene can lead to alterations in the effectiveness of many therapeutic and can lead to resistance to certain chemotherapeutic regimens. There are three main polymorphisms that affect P-gp function. The first polymorphism is an SNP within exon 21 that leads to an alteration of three amino acids in the gene leading to increased P-gp function. The second polymorphism tends to occur on exon 26 and it results in lower P-gp expression in the duodenum. The final

Table 1. Association Between Polymorphism and Cancers

Serial no.	Cancer	Genetic polymorphisms	Importance	References
1.	Colon, breast, pancreas, bowel cancer	CYP2 enzymes	CYP2A6*4 allele had decreased conversion of Tegafur into 5-FU.	[14, 15]
2.	Breast cancer, colorectal cancer and leukemia	GST enzymes	GSTA1B allele has increased survival for breast cancer.	[14]
3	Colorectal cancer	UDP-glucuronosyltransferase enzyme	UGT1A1*28 variant leads to higher levels of irinotecan in the blood leading to severe neutropenia and diarrhea.	[16, 17]
4	Lymphoblastic leukemia	TPMT enzyme	TPMT*3A and TPMT*3C alleles can cause hematopoietic toxicity.	[14, 16]
5	Colorectal cancer, breast cancer, head-and-neck cancer	DPYD enzyme	DPD is responsible for metabolizing 5-FU into inactive metabolites and patients with deficiency are associated with diarrhea, neurotoxicity, and myelosuppression.	[24]
6	Colorectal cancer, ovarian cancer, gastric cancer	MTHFR	MTHFR protein is important in folate metabolism and the synthesis of DNA and those with mutations are at higher risk for toxicity.	[23]
7	Bladder cancer, non-small cell lung cancer	ERCC1 enzyme	ERCC1 proteins are important for gene specific repair and high levels of the protein is associated with worse outcomes due to lesser response to platinum-based chemotherapy.	[23]
8	Ovarian cancer	ABCB1, ABCC2	SNPs in these transporters are associated with drug resistance to irinotecan.	[9, 23]

GST: glutathione S-transferase; 5-FU: 5-fluorouracil; MTHFR: methylene tetrahydrofolate reductase. TPMT: thiopurine methyltransferase; DPYD: dihydropyrimidine dehydrogenase; SNP: single nucleotide polymorphism.

polymorphism is in exon 12 and it does not have a direct effect on the expression of P-gp. All three of these polymorphisms affect the way that chemotherapeutic agents function. For example, doxorubicin is a major substrate for the P-gp transporter and the presence of the above-described polymorphisms leads to lower plasma levels of doxorubicin. BCRP is another member of the ABC transporter family and an SNP on exon 5 has been identified that leads to decreased BCRP levels and decreased clearance of medications. Bicalutamide is an anti-androgen that blocks the effects of androgen and is used in the treatment of prostate cancer which is excreted from cells by p-gp and BCRP. SNPs in BCRP have been shown to lead to increased levels of bicalutamide in their plasma leading to toxicity from the chemotherapy [9].

Polymorphisms not only lead to altered metabolism or transport of drugs, they can also lead to predisposition of patients to certain cancers. The identification of these polymorphisms can be useful as they can be targeted by specific therapies. The fusion of the bcr-abl protein is a known cause of chronic myelogenous leukemia (CML) and causes the loss of regulation of the tyrosine kinase. This leads to uncontrolled cell growth eventually causing tumor growth. The knowledge of the cause of this cancer allows physicians to prescribe tyrosine-kinase inhibitors as treatment [25].

Recent Developments in the Field of Genetic Polymorphisms

As genetic polymorphisms continue to present an ongoing challenge and opportunities for clinicians in the treatment of

patients, genotyping of well-known polymorphisms should be comprehensively studied and should be widely used for treatment plan. One development in the field of genomics for the purpose of identifying genetic variation is Genome-Wide Association Studies (GWAS). In GWAS, millions of genetic variants in the genomes of many individuals were tested to identify connections between what is present on the gene and the phenotype of the patient. This process has led to massive progress in the field of personalized medicine. The way in which GWAS works is first by the identification of a disease to be studied followed by genotyping using SNPs or whole genome sequencing association tests are performed in order to determine the areas in which the phenotype is associated with and eventually, the target genes are identified using chromatin immunoprecipitation and chromosome conformation capture method. GWAS has been used to identify hundreds of disease-associated SNPs [26-28]. GWAS can be applied in the clinic to predict the presence of a disease and how a patient may react to medication.

Another recent technology in the field includes mutation-specific therapies. This form of treatment focuses on prophylactically identifying specific mutation in patients and using that knowledge to develop a drug specific to the mutation. For example, in patients with a class III *CFTR* gene mutation, the sodium gate is dysfunctional causing a buildup of mucus. This specific mutation was localized in patients and the medication ivacaftor was developed to target the mutation. Ivacaftor does not target the loss of a sodium gate or any other *CFTR* mutation; it is specific to patients with the class III mutation [29, 30]. By developing medicines that have specific targets, there is an increase in efficacy of medication and a decrease in side effects.

Current Trends and Future Directions

The direct application of GWAS and other DNA sequencing techniques continues to enhance the field of personalized medicine. Personalized medicine centers around the concept that nuances in individuals' genomes make it necessary for medicines that are tailored to their specific genetic variability. Personalized medicine continues to grow in popularity as it addresses a defect in traditional medical practice. After observations of the way patient's individual pharmacokinetic profile can affect the way they can react to drugs, there has been a push for the development of early surveillance protocols to prophylactically prevent patients from having adverse reactions. This new way of treatment also emphasizes that diseases can be detected early on by examining personal thresholds instead of population thresholds [30].

Another emerging form of personalized medicine is the usage of patient-derived cellular avatars. By harvesting cells from an individual and creating induced pluripotent stem cells, researchers can exam a patient's genetic makeup outside of the patient. These personalized models are allowing researchers to even create partial organs of the patient which allows testing of treatments in a safe and controlled manner. This is especially beneficial in oncological treatments as this method allows for the replication of tumors that are specific to the patient. This technology allows for personalized cancer treatment and allows researchers to screen for polymorphisms that may predispose the patient to adverse reactions from chemotherapy. It also allows for the development of new medications that are specific to the profile of the patient's tumor [30, 31].

TRACERx is another example of the application of personalized medicine and evidence of the shift towards this type of medicine. This study shows that circulating DNA in the patients with small cell lung cancer can be analyzed and used to determine how the tumor is developing. This technology is allowing physicians to precisely select medications based on the profile of the tumor and monitor the development of resistance [30, 32].

Many health care professionals are also interested in using apps to collect health data from patients in order to make a data-base of genomic traits that can be applied to larger subgroups of populations [30]. The Vanderbilt Ingram Cancer Center developed an app called SMART precision care medicine which is designed to synchronize the patient's chart and genomic information to a set of data from a population with the same disease. The purpose of the app is to quickly provide resources to the physician and patient regarding the specific genetic profile of their disease [33, 34]. This app represents the necessity in medicine of speed and access to information in order to accurately treat a disease.

Personalized medicine has the capability of changing the face of modern medicine. By determining whether patients are at risk of adverse reactions or have resistance to a medication, the trial-and-error period of prescribing medication can be completely avoided leading to a drop in cost of medication for patients. Furthermore, patient adherence to taking prescribed medications will be higher if there is a guarantee that the medication will work. The widespread acceptance of personalized

medicine as the new standard of care is dependent on a multitude of factors. Genetic screening and data collection must become the norm in clinical practice in order to streamline the prescription practice. This process is dependent on the development efficient and cost-effective methods of screening and new methods to quickly produce medications [35].

Conclusions

The success of treatment is dependent on prescribing the right medication to a patient and this is all the more important for oncological patients. Avoiding the development of drug resistance and other adverse side effects is ideal for a physician and their patient. The method by which this possible is through the identification of genetic polymorphisms and their linkages to mutated proteins. The usage of GWAS, patient-derived cellular avatars, and TRACERx are useful in the development of personalized medicine which is targeted to the genetic profile of the patient. It is integral that there is a continued emphasis on this field as it presents major advantages to both the patient and physician.

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Conflict of Interest

None to declare.

Author Contributions

Aneesha Choudary Gummadi: study design, data analysis, and manuscript writing. Achuta Kumar Guddati, MD: study design, data analysis, and manuscript writing. All authors have read the manuscript and agree to the content.

Data Availability

The authors declare that all data used in this manuscript are publicly available.

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