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# Drug Gene Interaction

***Mr. Shubham Zankar[1], Mr. Dnyaneshwar Patil[2], Dr. Sonali Uppalwar[3]***

*Ideal institute of Pharmacy, Posheri, Wada.*

**Abstract**

When taking several drugs at once, there may be unanticipated drug interactions that result in negative side effects or impair the effectiveness of treatments, ultimately raising healthcare expenses. Predicting and avoiding some of these interactions has been made easier by a greater understanding of how medications are transported throughout the body and metabolised by enzymes like cytochrome P450.

Additionally, pharmacogenetics—the study of how individual genetic variations and medical conditions like kidney or liverdisease can affect drug behaviour and make interactions more unpredictable and potentially harmful—is receiving increased attention from researchers. Because of this, regulatory bodies now demand more thorough testing of drug interactions, particularly when there are genetic variations and several medications. Software tools have been created for everyday healthcare to notify physicians of possible druginteractions, and there is a movement towards prescribing methods that are more individualised. Better training for medical professionals, more intelligent electronic prescription systems, and the use of models to adjust medication dosages according to the individual characteristics of each patient are all examples of this.

## INTRODUCTION :

Numerous factors can impact a drug's effectiveness, including concurrent use of other medications, nutrition and diet, age and sex, underlying medical conditions, and even genetics.[1,2] Individual genetic variations can influence how a drug is processed and reacted to by the body. This may alter the medication's efficacy or safety in certain situations.[3,4] Pharmacogenetic (PGx) testing before beginning medication has been shown to help reduce the risk of negative side effects.[5] A person's metabolic phenotype, or how their body will react to specific drugs, can be predicted using their genes(genotype). However, sometimes their body's actual reaction to the drug differs from what we would anticipate from their genes alone. Phenoconversion is the term for when this occurs due to factors other than their DNA, such as other medications, illnesses, or lifestyle choices.[6] For instance, if a person has poor CYP2D6 metabolism, which means their body doesn't produce much of this enzyme, then prescribing a medication that blocks CYP2D6 won't help because there isn't much of an enzyme to block in the first place.[6]

Genetics has long been a useful tool for studying biology. One important method, called forward genetics (also called classical genetics), begins by searching for a particular characteristic or alteration in an organism, usually something that manifests under particular experimental circumstances. Following the identification of that trait, researchers attempt to identify the gene or genes that cause it. By examining the consequences of variations in genetic sequences, this technique has assisted researchers in determining the functions of numerous proteins.[7,8] One kind of enzyme produced by recombinant technology is microbial transglutaminase. It creates solid bonds both inside and between proteins, acting as a biological glue. In particular, it connects the side chain amide group of glutamine in proteins to the ε-amino group of the amino acid lysine.Proteins' structure is strengthened by this crosslinking, which also alters their stability or texture.[9]

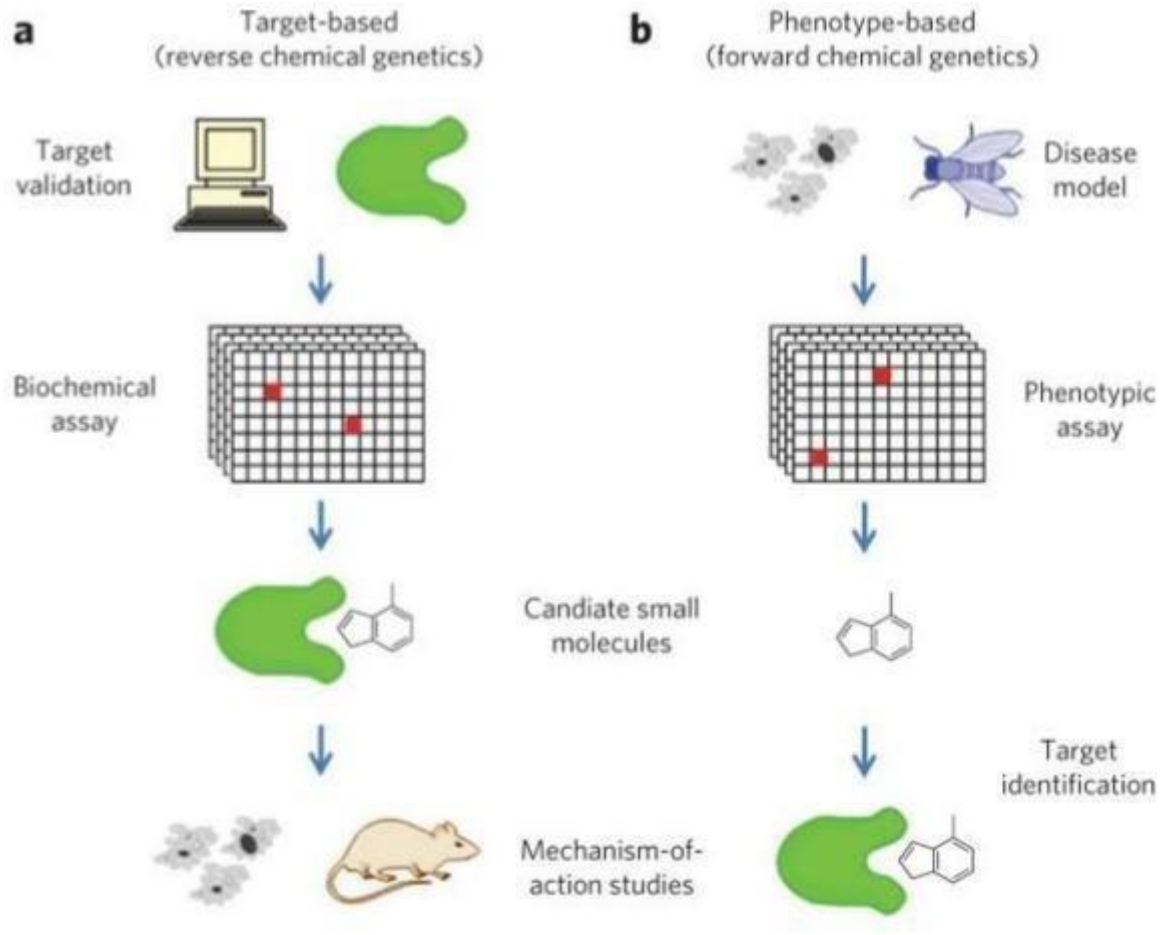


*Figure 1. Mechanism-of-action and target identification in chemical genetics*

## Approaches to target identification:

Three different and complementary methods for identifying a small molecule's protein target will be discussed in this review: genetic interaction and direct biochemical techniques techniques as well as computational inference techniques.[10]On the other hand, computers can use pattern recognition to generate target hypotheses. They accomplish this by contrasting the effects of tiny molecules with those of well-known medications or genetic alterations.[11,12]

***Genetic interaction and genomic methods :***

Using genetic and genomic methods for target identification makes use of the relative simplicity of working with DNA and RNA to facilitate high-throughput measurements and extensive genetic modifications. These techniques frequently depend on the idea of genetic interaction, which states that the existence or lack of one gene affects the effect of another. This idea involves generating hypotheses regarding possible therapeutic targets by using genetic modifiers, which are genes that either enhance (worsen a phenotype) or suppress (alleviate a phenotype).[13] Using genetic tools and integrating knowledge from RNAinterference (RNAi) and small-molecule treatments, a promising newapproach to drug target identification has emerged.

Researchers can test the effects of each method on cells and search for instances where they cause the same alterations by comparing the two methodsside by side. This makes it simpler to find possible targets for novel treatments by identifying which genes or proteins may be in charge of a given effect.[14,15] Mammalian cells are becoming a more prominent focus of genetic target-identification efforts. For example, clones of cells that are resistant to typically toxic substances have been studied by researchers using transcriptome sequencing (RNA-seq). They were able to determine the intracellular targets of those compounds by looking at these resistant cells.[16]Gene expression patterns have recently been used by researchers to determine the mechanisms of action of various medications, demonstratingthe close relationship between genetic tools and computer-based techniques. For instance, researchers can match medications to their effects on gene activity by using transcription profiling data from the Connectivity Map.[17]

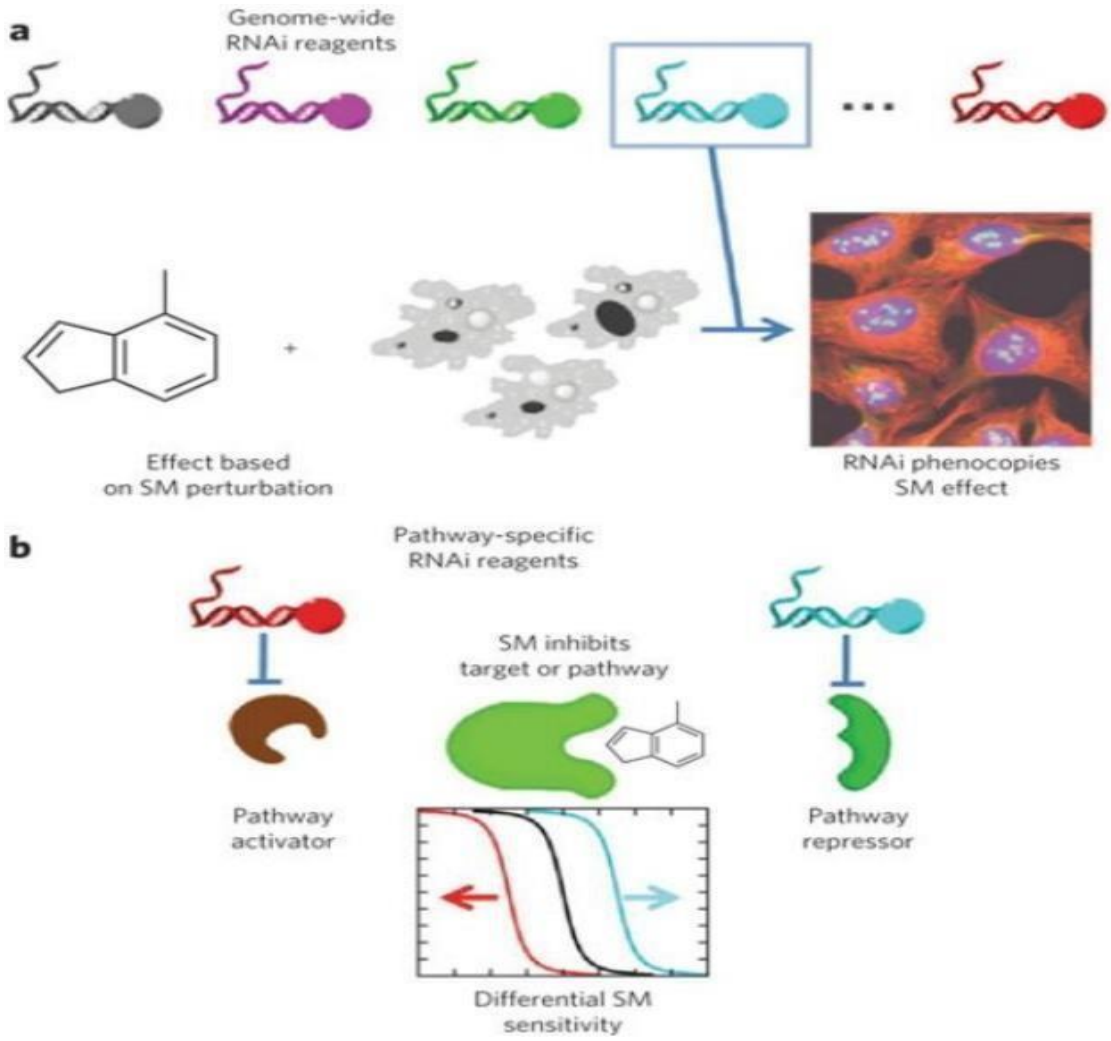


*Figure 2. Illustrations of RNAi-based methods for target-identification and mechanism-of-action [18,19]*

## Computational inference methods :

Finding the proteins that small molecules target requires the use of computational techniques. In addition, theyfacilitate the analysis of genetic and proteomicstudy data. In order to reposition medications or comprehend unexpected side effects brought on by off-target interactions, these tools are particularlyhelpful in identifying newtargets for currentlyavailable medications.[20,21] Ligand-based techniques predict which proteins a compound may interact with based on its chemical structure. However, in order to comprehend howsmall molecules might attach to proteins, structure-based approaches concentrate on their three-dimensional shape.[22,23] Researchers discovered that modulatoryprofiles could reveal extra relationships that the other approaches missed when comparing modulatory profile clusters with gene expression and structure-based profiles. One technique, called Bioactivity Profile Similarity Search (BASS), links small molecules to their possible targets by using information about how cells react to various dosages of compounds.[24]

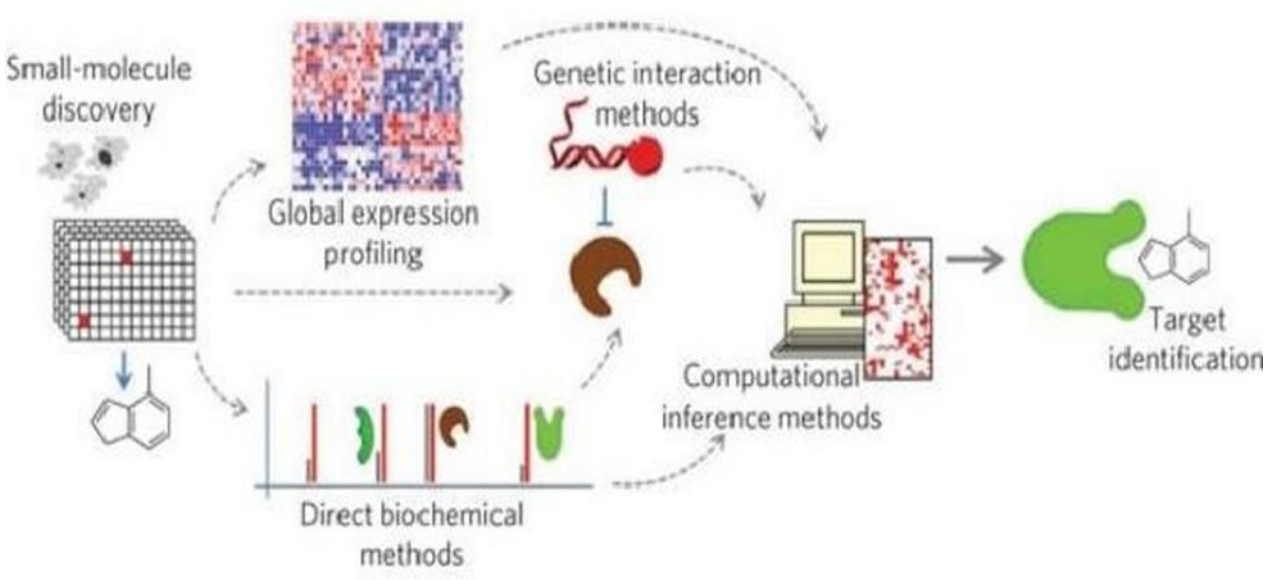


*Figure 3. Illustration of a conceptualworkflow for integrated target- identification and mechanism of action studies*

**Drug–drug-metabolizing enzyme gene interactions (DDMEGIs) Inhibitory interactiion :**

Take rabeprazole, a drug that is broken down by the CYP2C19 enzyme. Fluvoxamine, a medication that inhibits CYP2C19, dramatically raised the blood levels of rabeprazole in

individuals with normal or slightly decreased enzyme activity (caused by their genes).[25] Individuals with specific genetic mutations (such as CYP2C192 or 3) may not react as well to clopidogrel, particularly if they are also taking proton pump inhibitors (PPIs), which disrupt the medication's action. Clopidogrel may become even less

effective if you take another medication, such as a calcium channel blocker.[26,27]

**Induction interaction :**

Prodrugs function differently; more active drug is produced if metabolism rises (as a result of enzyme inducers or GOF variants). People with the CYP2C1917 variant, for instance, convert more clopidogrel into its active form, which may reduce the risk of heart attacks but may also increase bleeding.[28,29]

**Phenoconversion interaction :**

Medication can "normalise" a person's drug-processing behaviour, which is known as phenoconversion. People who have fast CYP2D6 metabolism, for instance, may not fully benefit from nortriptyline. However, CYP2D6 inhibitor paroxetine can slow metabolism and restore nortriptyline levels to a therapeutic range.[30]

**Variations in drug response :**

Individuals frequently react differently to drugs, and these variations in a drug's effectiveness or adverse effects may be brought on by inherited characteristics or things that have evolved over time. In the end, each patient's reaction is distinct.[31] Finding the appropriate dosage can be challenging due to these individual variations, particularly since most medications only work well for 25% to 60% of people.[32] Many patients don’t fully respond to the first treatment their doctor recommends. For example, about 38% of people with depression, 40% with asthma, 43% with diabetes, 50% with arthritis, and even 75% of cancer patients don’t see any benefit from their initial treatmen.[33 ] The way a medication functions or is processed can be impacted by genetic variations in how our bodies absorb and process medications. A person’s reaction to a medication can be influenced by even minute variations in their DNA, such as a single base (SNP) or a collection of them (haplotypes).[34,35]

**Influence of polymorphisms in genes encoding phase-I drug metabolism ng enzyme:**

**Cytochrome P450 2D6 :**

People's reactions to certain medications can be significantly impacted by genetic variations in the CYP2D6 gene; some may require up to ten times the same dosage to achieve the same result.[36] Several liver enzymes convert tamoxifen into its active forms, 4-hydroxytamoxifen and endoxifen. The most significant of these, CYP2D6, regulates the rate at which this process proceeds.[37] Codeine is a common painkiller that gets converted in the body to morphine, which provides the actual pain relief by acting on mu- opioid receptors. Morphine is about 200 times stronger at binding to these receptors than codeine.[38] Variants of the CYP2D6 gene *10, *17, and *41 typically function normally, but occasionally they are associated with slower or

decreased drug metabolism.[39] Up to 65% of people in the Chinese population have the CYP2D6*10 gene variant. Although the enzyme's activity is greatly decreased by this variant, it still functions.[40]

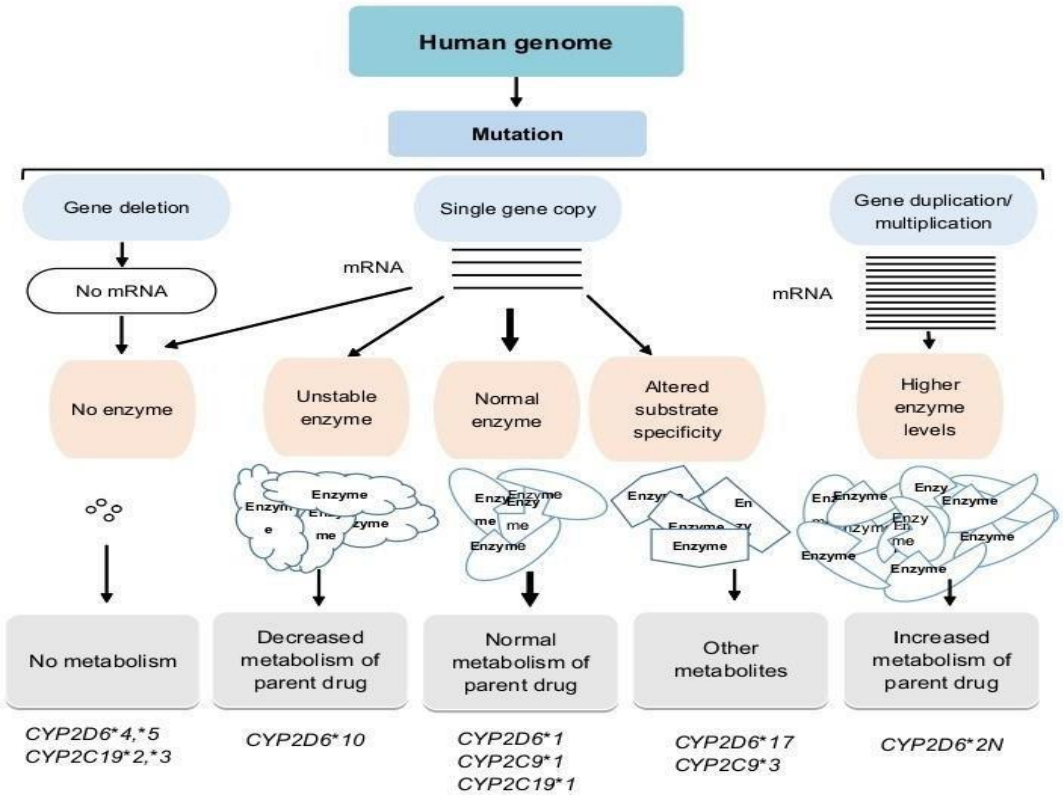


*Fig.4.An overview of important consequences of genetic polymorphisms in the CYPs*

## Conclusion :

Drug-gene interactions (DGIs), which affect how people react to drugs depending on their genetic composition, are essential to personalised medicine. Drug efficacy and toxicity can be greatly impacted by variations in the genes encoding drug-metabolizing enzymes, drug targets, transporters, and receptors. Comprehending these interactions minimises side effects and maximises therapeutic results by optimising medication selection, dosage, and treatment duration.

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