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GENE AND DISEASE: AN ‘‘OMICS’’ AS THE PILLARS OF SYSTEMS MEDICINE

Aaishwarya Deshmukh*

Smt. Kashibai Navale College of Pharmacy, Pune-411048, Maharashtra, India.

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***Corresponding Author**
Dr. Aaishwarya Deshmukh
Smt. Kashibai Navale College of Pharmacy, Pune-411048, Maharashtra, India.

ABSTRACT

In the age of systems medicine, the pathological set of connections, genetic mutations, allied anomalous pathways, and a response of drug for rectification of the abnormalities/disease are integrated transversely with the human biology systems by employing varied approaches of genomics, epigenomics, transcriptomics, and proteomics technologies. Pharmacogenomics studies the variation in human genome which is employed to predict responses to a specific drug or class of drugs. In recent years with the growth of pharmacogenomics, the concept of personalized medicine has becomes more often accessible in clinic settings for patient care. Most importantly, the rational case for genetics-specific drug selection and dosing is considered more established than the handy list of drugs for which outcomes are demonstrably improved. Thus significant accomplishment is possible with an interdisciplinary approach of genetics, technological and therapeutic measures establishing “OMICS” technologies as the pillars of systems medicine.

KEYWORDS: OMICS, Gene, Disease, Genetic variability, Drug response, Pharmacogenetic.

INTRODUCTION

A disease is not only a straightforward consequence of an abnormality in a single gene, but rather the interplay of multiple molecular processes the relationships of which are encoded in the interactome, a network that integrates all physical interactions within a cell, from protein-protein to regulatory protein–DNA and metabolic interactions. Disease-associated proteins interact with each other and they tend to cluster in the same neighborhood of the interactome, forming a disease module, a connected subgraph containing all molecular determinants of a disease. The accurate identification of this corresponding disease module represents the first

step toward a systematic understanding of the molecular mechanisms underlying a complex disease. The interactome and our knowledge of disease-associated genes still remain incomplete despite impressive advances in high-throughput interactome mapping and disease gene identification which prompts us to ask to what extent the current data are sufficient to map out the disease modules, the first step toward an integrated approach toward human disease.[1]

Most phenotypes reflect the interplay of multiple molecular components that interact with each other[2-5], many of which do not carry disease-associated variations and identifying sequence variations associated with specific phenotypes represents only the first step of a systematic program toward understanding human disease. Thus, we must view disease-associated mutations in the context of the human interactome, a comprehensive map of all biologically relevant molecular interactions.[5-9] But still there is limitation by several conceptual and methodological issues in the predictive power of the current network based approaches to human disease. First, 20% of all potential pair wise protein interactions in the human cell are covered through high-throughput methods[8-11], which means that disease mechanisms relying on interactome maps that are 80% incomplete is needed to be discovered. Second, the list of disease genes whose mutations have a causal effect on the respective phenotype traditionally captures the genetic roots of a disease. The disease proteins (the products of disease genes) tend to interact with each other, forming one or several connected subgraphs called the disease module are not scattered randomly in the interactome (Figure 1A) and this agglomeration of disease proteins is supported by a range of biological and empirical evidence[6,12,13] which has fueled the development of numerous tools to identify new disease genes and prioritize pathways for disease relevance.[7,8,14-22] Third, the relationships between distinct phenotypes are currently uncovered by identifying shared components like disease genes, single-nucleotide polymorphisms (SNPs), pathways, or differentially expressed genes involved in both diseases that has resulted in the construction of “disease networks,” unveiling the common genetic origins of many disease pairs.[6,23] Up till now, shared genes offering only limited information about the relationship between two diseases.

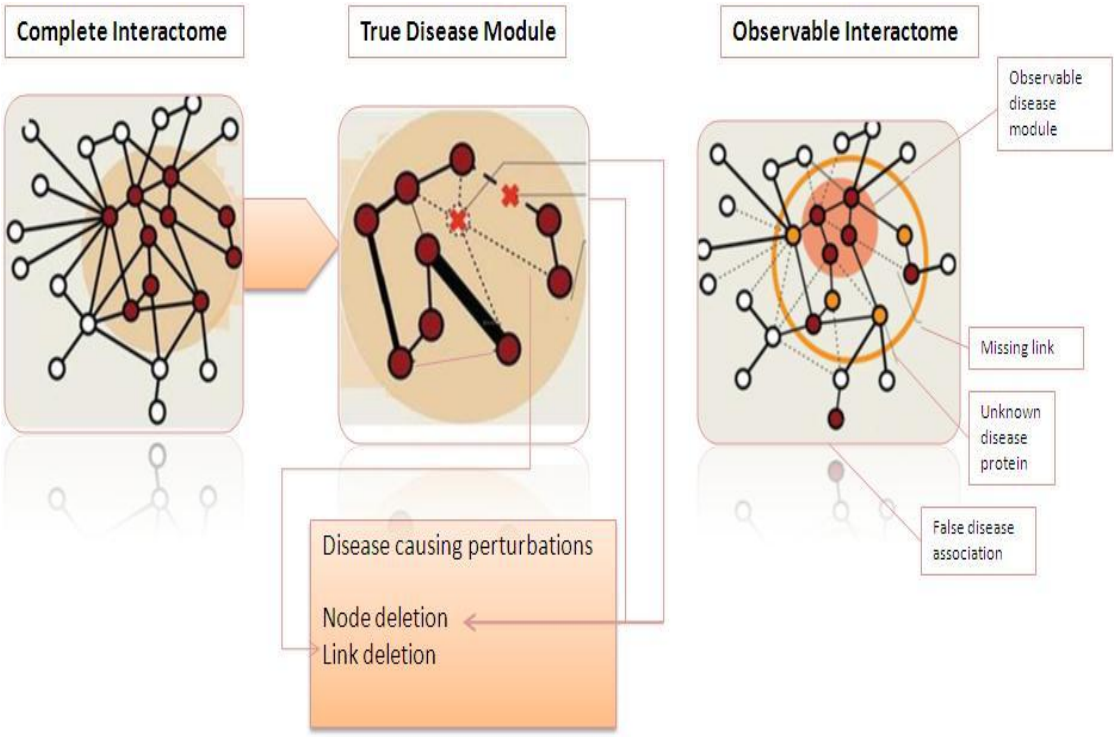

Figure 1A: Figure showing transition from the human interactome to disease modules.

1. An ‘‘Omics’’ view of drug development

The pharmaceutical industry is said to have a love/hate relationship with the fields of pharmacogenetics and pharmacogenomics. Pharmacogenetics and pharmacogenomics save pipeline drugs by identifying subsets of the population for which they work best but also threatens to increase the complexity of new drug applications, fragment markets, and create uncertainty for prescribers who simply do not understand or have time to master ‘‘personalized medicine.’’ Pharmaceutical developers and regulators have been careful in creating strategies for using genetics in drug development, and recently FDA has begun to establish preliminary rules for pharmacogenetic testing and should combine a growing public academic effort in pharmacogenetics and pharmacogenomics which will help flesh out the basic science underpinnings of the field to create a solid foundation for future use of genetics in drug development.[24] The management of large amounts of information, even about the basic players, in gene-drug-disease interactions is one of the major difficulties for basic research in pharmacogenetics and pharmacogenomics. There are roughly 30,000 human genes, more than 5,000 drugs on the market, more than 4,000 diseases in the Medical Subject Headings, and uncountable numbers of measurable phenotypes (laboratory measurements, clinical measurements, symptoms, side effects, and signs) related to drug response. Moreover, a recent study estimates that the PubMED database of medical literature contains

about 200,000 articles related to genes and genes to drugs in one way or another (from a total of more than twelve million citations)[25] which clearly suggests the need for supporting[1] assessing existing knowledge and generating new hypotheses.

1.1 A challenge for Pharmacokinetics

Genes involved in the metabolism of drugs, including the major genes involved in the cytochrome p450 system: CYP2D6, CYP3A4, CYP2C19, CYP2C9, CYP1A2, and CYP3A5 dominates the existing literature on pharmacogenomics which are significant for the pharmacokinetics of many drugs, and there are online clinical references that compile the association of clinical drug interactions with shared metabolism by these and other genes (see, for example, http://medicine.iupui.edu/flockhart/table.htm). The conjugating enzymes (acetylases, uridinylases, methyltransferases, sulfotransferases) and transporter genes (particularly, MDR1, organic anion, and cation transporters) are other genes that are on the list of ‘‘usual’’ pharmacokinetics suspects. The effects of these same genes on other drugs were checked by scientists once important drug effects were discovered and the evidence for their importance increased but undiscovered additional genes in these or other families is not entirely clear. Nevertheless, having the human genome sequence is an added advantage that the complete set of genes is known. The existence of homologs to well-known drug metabolizing genes allows for systematic evaluation of the presence and importance of their gene products and so it would be rather easy to discover new variations (either homologs or post-translationally modified products) that have important effects. Recently, there are tools necessary to identify and characterize the complete set of genes (cytochromes, conjugation enzymes, and transporters) that are liable to be important for the metabolism of all drugs. On one hand gene sequence analysis gives the candidate genes in the genome while Microarray expression experiments allow us to evaluate mRNA expression patterns in different tissues and Proteomics (mass spectrometry) allows characterization of the protein products and their further localization. Therefore, the complete characterization of all genes available for the metabolism of drugs, their gene expression, protein translation, modifications, and localization is one magnificent challenge for pharmacogenomics. Though variation in these genes represents only half the story for pharmacogenomics, it is a half that seems to be within reach with the completion of the human genome, and the related ability for identification of all the enzymes and transporters present in the genome. The proposition of such a complete catalog for drug development would be significant wherein with a finite list of genes relevant

to pharmacokinetics; new drugs could be evaluated with respect to their likely interactions with gene products.

1.2 A challenge for pharmacodynamics

Metabolism seems to be carried out by a relatively well defined and identifiable subset of genes, drug action occurs on a much larger and more diverse set of target genes rendering the impact of genetic variation on drug response and pharmacodynamics harder to assess. Thus, the probabilities of new target genes being fully characterized in terms of their functional characteristics are lower. Conversely, G-protein coupled receptors (GPCRs), taken as a group, are the most common set of targets as indicated by recent surveys of prescription drugs which include receptors for histamine (allergy and antacid medications), Angiotensin (hypertension), α and β adrenoceptors (asthma, hypertension, cardiac), insulin (diabetes), serotonin (depression), and many others. Though the drugs acting on these receptors are quite diverse, still they can be categorized based on their interaction with the receptor (activator or inhibitors, for example). Thus an increased pace of publication in the public domain has been raised on the genetic variations in these receptors and how they relate to phenotypes. Moreover, apart from GPCRs, there are a large number of drug targets whose genetic variation remains to be assessed and catalogued. Opportunely, common variations in human genes are needed to be catalogued once, so focused efforts on genes of pharmacologic interest (such as are undertaken in academic and industrial efforts focused on particular targets) as well as general surveys of variation (such as in the HapMap project)[26] are likely to yield the fundamental list of common variations individually - single nucleotide polymorphisms (SNP) as well as common combinations of these variations (Haplotypes). The only remaining challenge is to characterize the functional consequences of these variations for drug response for which high throughput genomic technologies can be considered critical. The important consequences of drug exposure on gene expression are not missed and is ensured by the ability of mRNA expression arrays to simultaneously measure the mRNA levels of all genes in a particular cell type. Proteomic technologies should be developed for assaying levels and activities of gene products in a comprehensive, cost-effective manner. The work to be done in this regard is considerable, and so the real issue becomes prioritization of effort.

1.3 Identifying research priorities

A new research ethic is being implemented recently for the success of ‘‘omics’’ initiatives to devise relatively in expensive high-throughput experiments and collect comprehensive data sets and these data are stored in databases with appropriate search and comparison functionalities. These databases are then used to evaluate opportunities for new knowledge by mining the databases to form specific testable hypotheses and subsequently returning to the lab for confirmation which serves two-fold advantage. First, the use of comprehensive data sets collected without particular hypotheses in mind leads to a less biased, more objective search for promising hypotheses. Secondly, these data sets allow the resulting hypotheses to be very focused and straightforward to test with confirmatory experiments, thus increasing the overall cost-effectiveness of the scientific enterprise. Thus *F*omics approach to drug discovery and development will result in effective use of genomic information to accelerate our ability to prescribe the right drug at the right dose on the first try as is suggested by the pharmacology research community.

2. GENE AND DISEASE

Genome-wide association studies are rapidly unraveling the role of genetic factors in the pathogeneses of common diseases[27] and that these advances will lead to personalized medicine, in which preventive and therapeutic interventions for complex diseases are tailored to individuals based on their genetic profiles.[28,29] Personalized medicine already exists for monogenetic disorders in which genetic testing is the basis for informing individuals about their future health status and for deciding upon specific, often radical interventions such as lifetime dietary restrictions and preventive surgery. However, complex diseases differs in etiology than that of monogenic diseases, and hence translating the new emerging genomic knowledge into public health and medical care is one of the major challenges for the next decades.[30,31] A predictive test or prediction model is an essential prerequisite for personalized medicine to become feasible that can discriminate between individuals who will develop the disease of interest and those who will not and the level of discrimination required in clinical care and public health applications depends, among other things, on the goal of testing, the burden of disease, the costs of disease, the availability of (preventive) treatment and the adverse effects of false-positive and false-negative test results.

2.1 Genetic testing in common diseases

The genetic origin of common complex or multifactorial diseases differs essentially from that of monogenic disorders which are completely or predominantly caused by DNA variations in

one single gene, and hence, carriers of mutations typically have distinctly higher disease risks than non-carriers. Complex diseases result from the joint effects of multiple genetic and environmental causes, with each factor having only a minor contribution to the occurrence of disease with risks of disease differing only in margin between carriers and non-carriers of risk variants of one single susceptibility gene, and prediction of disease based on a single genetic variant is considered not informative.[32,33]

The simultaneous testing at multiple genetic loci, known as genetic profiling implies genome-based prediction of complex diseases, the predictive value of which has been investigated in a few empirical studies to date, and this number is steadily increasing. These kinds of studies in disease like type 2 diabetes, coronary heart disease, myocardial infarction and age-related macular degeneration (AMD) showed limited predictive value so far, with the exception of the five susceptibility variants involved in AMD and the seven variants in hypertriglyceridemia.[34-37] However, the predictive value in these two studies are considered to be overestimated because of their performance in hyperselected populations not representative for clinical practice, comparing individuals with end-stage AMD with those without eye abnormalities and individuals with hypertriglyceridemia with normolipidemic individuals[36], prediction of these disorders is deemed promising as the individual variants have very strong effects compared to what is generally seen in common diseases. The genetic profiles that have been investigated empirically to date includes only a small number of mostly weak susceptibility variants that are not yet useful for the application in clinical medicine or public health. Simulation studies shows that the predictive value of a larger number of genes (up to hundreds) theoretically attain the same level as that of traditional risk factors predicting cardiovascular disease.[38,39], but it may not evidently become much better. Thus common diseases that are only partly influenced by genetic factors have a ‘natural’ limit to the predictive value of genetic profiling that can never be perfectly predicted by genetic testing.[38] For applications in health care, thus genetic profiling may become useful for the identification of individuals at increased risk of disease to the same extent as traditional risk factors do, that its predictive value may not be high enough for decisions about invasive, irreversible and expensive interventions or for presymptomatic diagnosis. Some interesting features of genetic profiles have also demonstrated in recent simulation studies that explain the reason for difficulty in the predictive value of a larger number of multiple weak susceptibility variants.[40,41]

2.2 Improving disease prediction

Testing multiple susceptibility variants alone may not yield perfect prediction of complex diseases and that it will improve the prediction of disease beyond classical risk factors is also not predictable. Studies have showed that genetic factors do not substantially improve the prediction of type 2 diabetes, coronary heart disease and prostate cancer although the construction of profiles consisting of genetic and environmental risk factors appears an obvious solution but again the number of genes investigated was small.[42-45] Nonetheless, from a theoretical perspective, it can be argued that a large number of genes will unlikely have substantial added predictive value over traditional risk factors if these variants predispose the risk factors. For example, genes associated with cardiovascular disease may also be involved in transitional outcomes such as dyslipidemia or hypertension or even smoking.[44,46] Genetic variants involved in intermediate factors will not remain significant when they enter in a regression model together with these intermediate factors as is according to the basic principles of epidemiological research. Disease prediction may be improved beyond traditional risk factors with the help of genetic variants when they are involved in unknown pathways or in pathways with immeasurable intermediate factors. Moreover, novel thus far unknown pathways may be more likely for some diseases than for others. A critical reminder is that gene discoveries may also identify new etiological pathways and novel intermediate biomarkers, which consequently may be stronger predictors of disease than the genetic variant that led to its identification.

2.3 Complete causal mechanisms

One of the paradigms in complex genetics is that the genetic prediction of common diseases can be substantially improved if genetic variants are identified with strong effects, either on their own or in interaction with other variants or with environmental factors, i.e. gene–gene or gene–environment interaction. However, perfect prediction of disease may only be achieved if the essential genetic and environmental factors in the causal mechanisms of the disease are understood. Rothman and Greenland[47] has defined a complete causal mechanism or a sufficient cause of disease as a set of ‘minimal’ (implying that all component causes need to be present for the disease to develop) conditions and events that inevitably lead to disease. E.g. when only one causal pathway is involved, the risk of disease is 100% when all component causes are present and 0% when one or more causes are absent. Chance or randomness does not exist in the Rothman and Greenland models of complete causal mechanisms.

Figure 1B shows schematic diagrams for complete causal mechanisms of monogenic and complex diseases. Figure 1 B(i) presents a sufficient cause diagram for Huntington disease; wherein there is only one causal factor i.e. CAG extensions in the huntingtin gene are a complete and sufficient cause for the development of the disease despite the fact that there may be genes that modify age of onset. Figure 1 B (ii) presents a complete causal model for PKU, which only occurs when homozygous carriers of mutations in the PAH gene are on a normal diet that includes phenylalanine. This model serves as a typical example of gene–environment interaction from a statistical perspective. For common diseases that result from multiple genetic and environmental causes, the complete causal mechanisms are by far more complex (Figure 1 B(iii)- 1 B(vi). They consist not only of a large number of different component causes, but a specific disease that may also result from different causal mechanisms. For example, a complex disease may be caused by the presence of four different risk variants in different genes (G1 to G4 in Figure 1 B(iii)), but in absence of one of the risk variants (G4) then still the disease may inevitably occur when instead four other genetic risk variants (G5 to G8) and an environmental risk factor (E1) are present (Figure 1 B(iv)). Therefore, for complex diseases, there are not one but many distinct combinations of risk factors that lead to disease development, with major single risk factors emerging in multiple combinations.

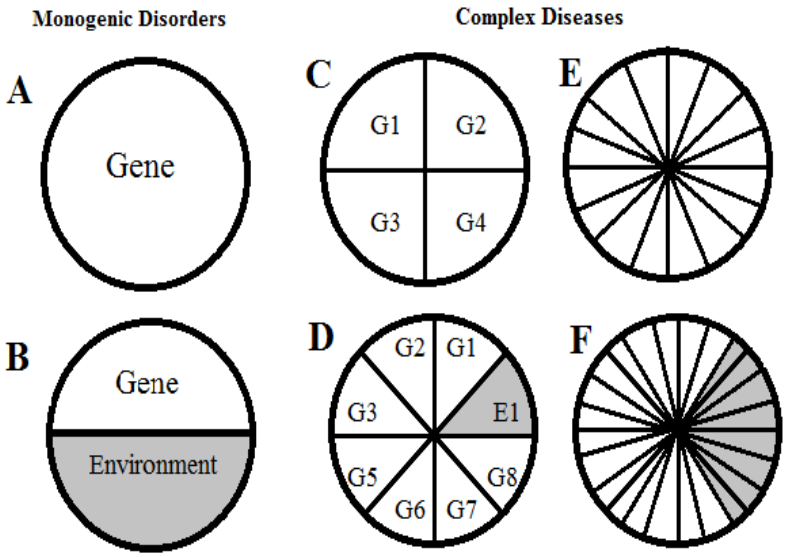

Figure 1B: Complete cause models or sufficient causes of disease development. Complete causal models for (A) Huntington Disease; (B) Phenylketonuria; (C–F). White areas refer to genetic factors and grey areas to environmental factors.

2.4 From causal models to disease prediction

The identification of specific combinations of causal factors among all possible combinations, namely identifying those combinations that inevitably lead to disease is implied by discovering complete causal mechanisms of common diseases. As most multi-factorial diseases are caused by a complex interplay of many genetic and non-genetic factors, the number of potential combinations of these many factors is extremely large and easily outnumbers even the size of large cohorts or consortia which can be exemplified by the simultaneous testing of nine genetic variants, with three genotypes each, gives 39 or 19 683 potential genotype combinations and the testing of 12 variants gives 531 441 combinations. When a genetic profile of 12 variants is tested in a cohort of e.g. 30 000 individuals, all cases as well as all controls will likely have unique profiles even when risk variants are common which has two implications. First, it will be very complicated to prove that the profiles that are found only among cases actually are complete causal mechanisms because it is extremely unlikely that the same combination of risk factors will be found in more than one person. Second, even if specific combinations are identified as complete cause mechanisms, still its usefulness for the prediction of common disease is much inadequate. Thus when combinations of risk factors are ‘unique’, only a few other persons in the world may have that exact same profile.[48]

3. GENETIC VARIABILITY IN DRUG RESPONSE

The complex interplay between multiple factors (including age, organ function, concomitant therapy, drug interactions, and the nature of the disease) and genetic background is responsible for variability in drug response. DNA sequence variations that are common in the population (present at frequencies of 1% or higher) are known as polymorphisms (not just “mutations”) and they influence the function of their encoded protein, thus altering human phenotypes. Amongst the various genetic variations, there are at least two common polymorphisms having a substantial influence on the interindividual variation in human metabolism: Single Nucleotide Polymorphisms (SNPs) and insertions/deletions (indels). SNPs are largely distributed polymorphisms in which a single nucleotide (A, T, C, or G) is altered in the genome sequence and accounts for most variations found in the genome. SNPs are nonsynonymous (or missense) if the base pair change results in an amino acid substitution, or synonymous (or sense) if the base pair substitution within a codon does not alter the encoded amino acid. Indels are much less frequent in the genome, especially in coding regions as compared to SNP. Most indels within exons (representative nucleotide

sequences that code for mature RNA), may cause a frame shift in the translated protein and so changes protein structure or function, or result in an early stop codon, which makes an unstable or nonfunctional protein. It is however imperative to state that the functional effects of structural genomic variants are not limited by SNPs and indels, but also related to others process such as inversion and multiple copies of genes (as observed in *CYP2D6*), and even the occurrence of a new gene-fusion products.[49]

3.1 Genetic polymorphisms influencing drug response

The pharmacokinetics (disposition and fate of drugs) and their pharmacodynamics (therapeutic and toxicological effects) depend on complex processes involving proteins codified by different genes influencing drug transport, metabolism, and mechanism of action and most genes contain casual variations in their nucleotide sequence developed during evolution. Variations located in a codifying region may lead to substitution of an amino acid in a specific position of a protein and consequently may affect protein function. Also when variations occur in a regulatory region, they may influence transcriptional and translational mechanisms with consequent modulation of gene product (mRNA and proteins) expression levels.[50] Polymorphism may be defined as variation in the DNA sequence with a 1% allelic frequency or greater in a population, while mutation states variation characterized by less frequency. Gene mutations and polymorphisms codify for enzymes characterized by different metabolic activity or receptors with different affinity for the drug and modify the pharmacological response in individuals or, in case of variations particularly frequent in some ethnic groups, even in a population. Genetic variations also involve several nucleotides or long DNA traits considered as large mutations and defined substitutions, insertions, deletions, amplifications and translocations apart from single base pair substitutions like SNPs.[50,51] Prototypes involved in pharmacogenetics refer to monogenic traits which consist of polymorphisms of a single gene codifying for a protein involved in the metabolism or in the effects of a drug that cause variable individual responses to this drug. an increased response and toxicity from drugs belonging to very different classes (e.g. anticoagulant, psycothropic and immunosuppressive drugs) or for the diminished response to prodrugs such as codein that requires metabolism to morphine to be active is caused by allelic variants of CYP proteins.[52,53]

3.2 Pharmacokinetic pharmacogenetics

The genes encoding enzymes and transporters involved in drug pharmacokinetics: absorption, distribution, metabolism and excretion (ADME) have been extensively researched and relevant allelic variants to drug treatment's outcome have been discovered. Enzymes carrying out the biotransformation of xenobiotics are classified as phase I or phase II. Phase I enzymes catalyze reactions like hydrolysis, reduction and oxidation, while phase II enzymes catalyze sulfation, acetylation and glucuronidation like conjugation reactions.[54] The majority of phase I reactions are catalyzed by the cytochrome P450 (CYP) enzymes. There are 57 cytochrome P450 (CYP) genes pseudogenes grouped according to their sequence similarity into 18 families and 44 subfamilies but only three of those families, CYP1, CYP2 and CYP3, catalyze most phase I reactions of drugs; over 75% of prescribed drugs are metabolized at least in part by three subfamilies: CYP3A, CYP2D6 and CYP2C.[55,56] The excretion of drugs is significantly enabled by Phase II reactions by considerably increasing the hydrophilicity of the substrate or deactivate highly reactive species which includes key enzymes like *N*-acetyltransferases 1 and 2 (NAT1 and NAT2), thiopurine *S*-methyltransferase (TPMT), and the uridinediphosphateglucuronosyltransferase (UGT) family and polymorphisms in these genes have been revealed to have clinical implications for a variety of diseases.[54]

3.3 Pharmacogenetics of drug-metabolizing enzymes

Most often prescribed drugs undergo biotransformation catalyzed by members of the CYP3A family (37% of the drugs), followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), and CYP2C8 (6%), while CYP2B6 and other CYP isoforms (CYP2A6 and CYP2E1) are responsible for the metabolism of 4% and 2% of the drugs, respectively. *CYP2C9* which is highly expressed in liver, metabolizes many weakly acidic substances like the anticoagulant warfarin, the anticonvulsants phenytoin and valproic acid, cardiovascular drugs like rosuvastatin and losartan, and several nonsteroidal anti-inflammatory drugs (NSAIDs). Moreover, many of these drugs have a narrow therapeutic index, and variations in CYP2C9 activity may be considered as one of the essential factor for adverse drug reactions. *In vitro* as well as clinical studies have established that the *CYP2C9*2* and **3* alleles are associated with significant and highly variable, reductions in intrinsic clearance depending on the particular substrate; for example, *CYP2C9*3* allele might be associated to up to 90% reduction in the enzymatic activity of the CYP2C9 protein. Higher incidences of adverse drug reactions like hypoglycemia from antidiabetic drugs, gastrointestinal bleeding from NSAIDs, and serious bleeding from warfarin treatment are observed with carriers of *CYP2C9*2* and

*CYP2C9*3* alleles as they are poor metabolizers and have high plasma levels due to low clearance of the substrate-drugs. Two null alleles lead to poor metabolizer (PM) phenotype and absence of functional CYP2C19 protein, whereas at least one functional allele is carried by extensive metabolizers. The prevalence of null alleles is about 3–5% to white and black populations and upto 20% of Asians are carriers of two null alleles e.g. two most common null alleles are *CYP2C19*2* occurring exclusively in Caucasians, and *CYP2C19*3* occurring chiefly in Asians.

The *CYP3A4* subfamily contributes to the metabolism of the most diverse group of substrates of all human P450 because of their flexible active sites which bind and metabolize many preferentially lipophilic, structurally large compounds, such as: the immunosuppressants cyclosporin A and tacrolimus, macrolide antibiotics like erythromycin, anticancer drugs like taxol, benzodiazepines, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors like simvastatin and atorvastatin, and anesthetics. Additionally, CYP3A4 is the only human drug-metabolizing P450 that demonstrates a significant sex difference e.g., women express approximately 1.5- to 2-fold more CYP3A4 and thus have higher *in vivo* clearance of several typical CYP3A4 drug substrates than men do. The functional effects of *CYP3A4* gene polymorphisms on drugs pharmacokinetic variability are still controversial in spite of a number of large-scale sequencing and phenotype–genotype correlation studies. However, *CYP3A4* basal and inducible expression phenotype might be influenced by other genes like: a) higher basal CYP3A4 expression and activity is induced by multiple drug resistance gene *MDR1 2677T (Ser893)* allele, whereas a higher rifampicin induction ratio in primary hepatocytes by 2677G allele; b) promoter or intron 1 regions associated with CYP3A4 basal and inducible expression levels locates pregnan X receptor *PXR* gene polymorphisms.[55] N-acetyltransferase type 2 (NAT2) which is a phase II drug metabolizing enzyme is responsible for hepatic bioconversion of major antituberculosis agent isoniazid (a pivotal agent in the treatment of tuberculosis, that remains a global emergency due to the growing prevalence of drug-resistant *Mycobacterium tuberculosis* and of *HIV* infection) to acetylisoniazid. *NAT2* gene is affected by a bimodal distribution polymorphism (acetylation polymorphism) which was portrayed after clinical observation of more frequently severe peripheral neuropathy and hepatotoxicity as adverse drug reactions to the slow-acetylators patients whose mean elimination half-lives is 180 min. in comparison with 80 min. for rapid-acetylators. Carriers of at least one wild-type allele (*NAT2*4*) or a high-activity variant allele (*NAT2*12*) have shown high NAT2 enzymatic activity (rapid acetylators), whereas two low-

activity variants are slow acetylators. Couturing isoniazid therapy means to increase isoniazid dose for rapid acetylators to achieve therapeutic efficacy and reduce dose for slow-acetylators to avoid adverse drug reactions while maintaining the desired antituberculosis effect.[57]

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Authors

All research done by the authors.

Conflict of interest

None.

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