Genetic Polymorphisms in Phase II Enzymes and Bioinformatics

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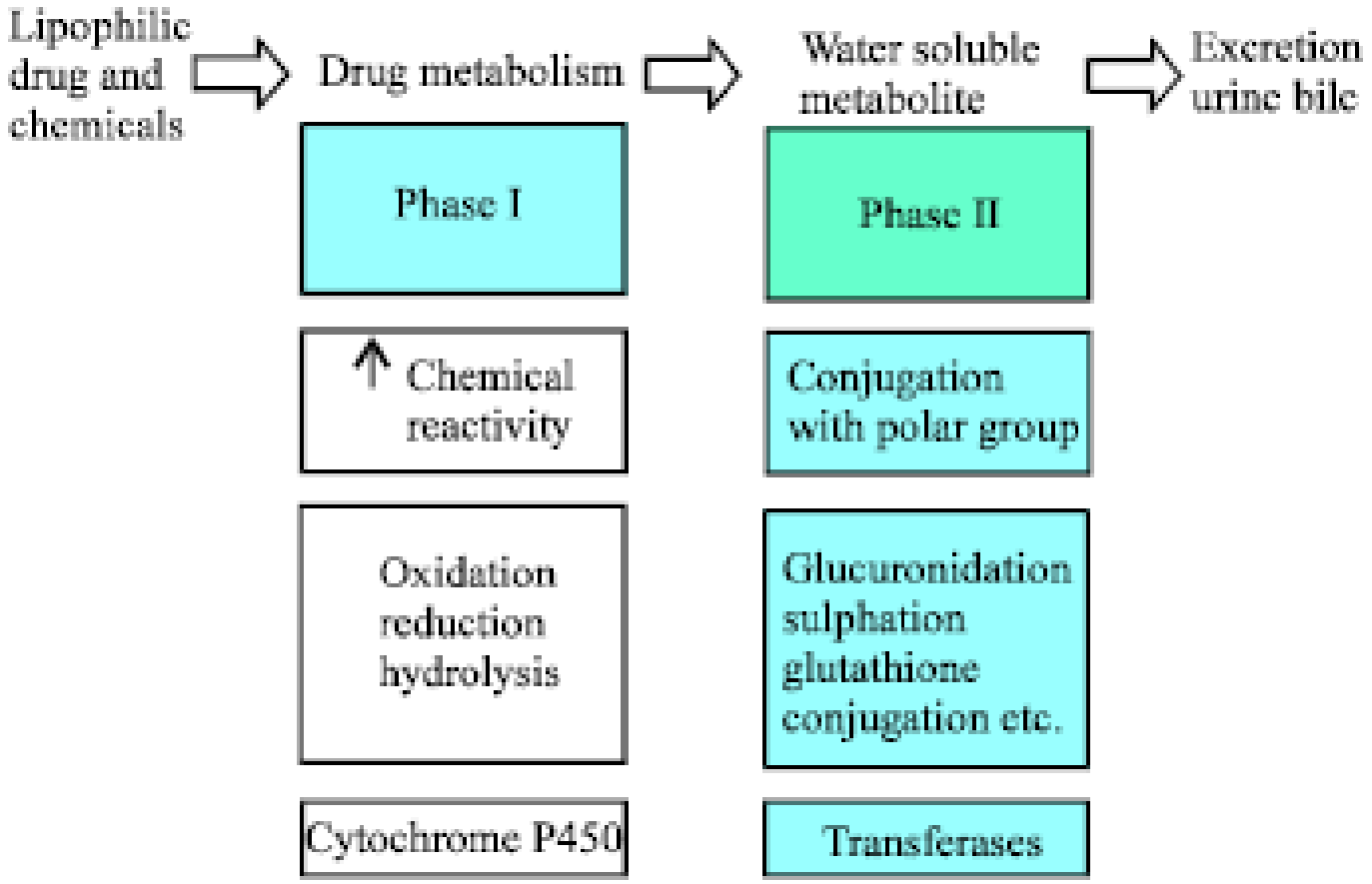
- Medicines are primarily used for treatment of disease.
- However, sometimes medicines have side effects.
- Side effects can differ for each individual depending on the medical condition.
- Diet, environment, physiological effects, gender, age and health are among the possible factors of this variability .
- But it's become increasingly clear that **genetics** can also be an important **factor** in terms of the efficiency or toxicity of the medicines.

PHARMACOGENETICS

- Pharmacogenetics has been defined as the study of variability in drug response due to heredity. In other terms, pharmacogenetics is defined as the study of genetic variations that cause a variable drug response, including the genetic polymorphism of drug transporters, **drug-metabolizing enzymes,** and drug receptors.

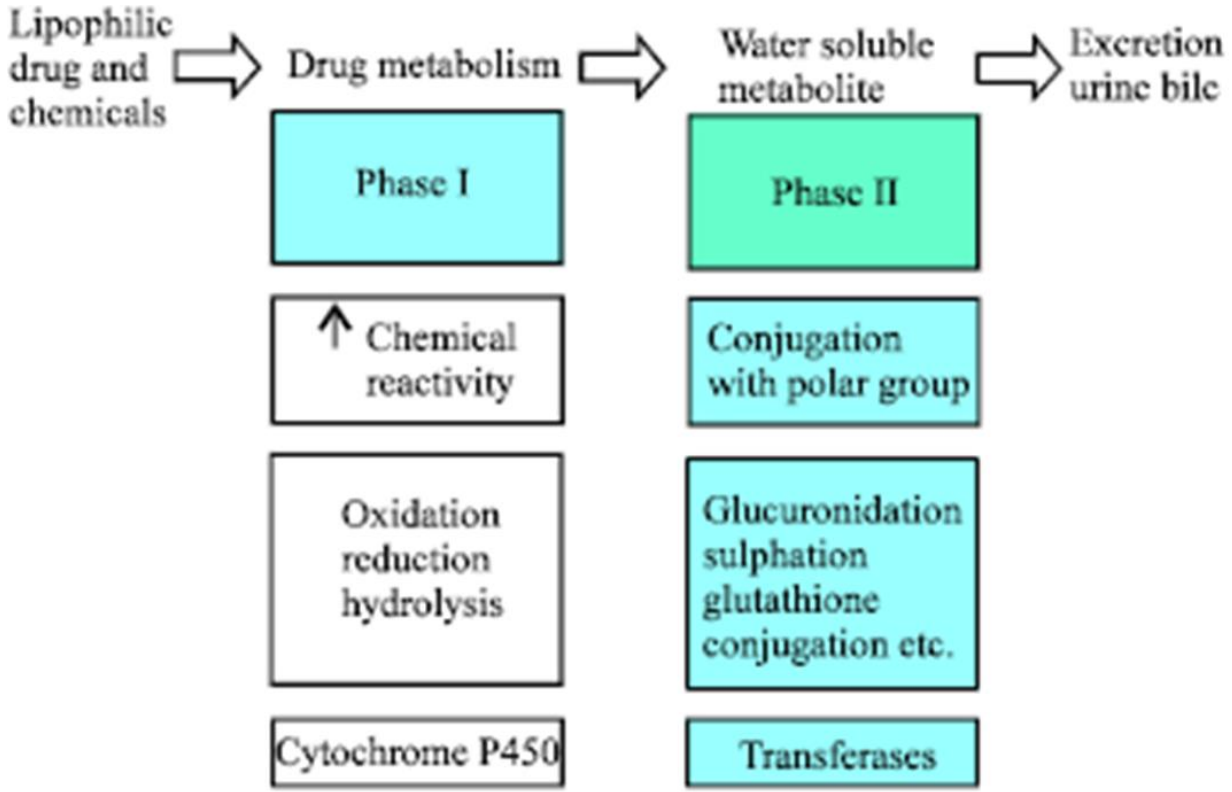
Drug metabolizing enzymes

- Phase I enzymes
- **Phase II enzymes**



http://higherimpactfactorjournals.blogspot.com/2015/03/role-of-phase-ii-drug-metabolizing.html

- Phase II drug-metabolizing diverse enzymes inactivate chemical carcinogens into less toxic or inactive metabolites. Several drugs change the rate of activation of carcinogens by changing the activities of phases I and II drug-metabolizing enzymes.



- The balance of activation reactions relies on the chemical structure of the agents in concern of this; genetic background, sex, endocrine status, age, diet, and the existence of various chemicals can be effected to this balance.

Phase II enzymes

- The reactive species are often detoxified by phase II drug metabolism enzymes , such as glutathione S transferases (GSTs), UDP-glucuronosyl transferases (UGTs), sulfotransferase (ST) and N-acetyltransferase (NAT).
- Phase II enzymes classically conjugate these **hydrophobic** intermediates to a water-soluble group, thus masking their reactive nature, and allowing subsequent excretion. Therefore, strategies that modulate the levels of phase II enzymes by either pharmacological or nutritional means can lead to enhanced elimination of reactive species.

Plymorphism in Phase II enzymes

- What is Genetic Polymorphism?

Genetic differences in drug metabolism are the result of genetically based variation in alleles for genes that code for enzymes responsible for the metabolism of drugs.

In polymorphisms, the genes contain abnormal pairs or multiples or abnormal alleles leading to **altered enzyme function**.

Differences in enzyme activity occur at different rates according to racial group.

Phase II enzymes

Enzyme	Substrate	Clinical Consequence
N-acetyltransferase (NAT1)	Aminosalicylic acids, aminobenzoic acid, sulfamethoxazole	Possible increased cancer risk Hypersensitivity to sulfonamides; amonafide toxicity; hydralazine-induced lupus, isoniazid neurotoxicity and hepatitis
N-acetyltransferase (NAT2)	Isoniazid, hydralazine, sulfonamides, amonifidide, procainamine, dapsone, caffeine	
Glutathione transferase (GSTM1, M3, T1)	Busulfan, aminochrome, dopachrome, adrenochrome, noradrenochrome	Possible inc cancer risk; cisplatin induced ototoxicity
Glutathione transferase (GSTP1)	13-cis retinoic acid, busulfan, ethacrynic acid, epirubicin	Possible inc cancer risk
Sulfotransferases	Steroids, acetaminophen, tamoxifen, estrogens, dopamine	Possible inc or dec cancer risk; clinical outcomes in women receiving tamoxifen for breast cancer
Catechol-O-methyltransferases	Estrogens, levodopa, ascorbic acid	Decreased response to amphetamine, substance abuse, levodopa response
Thiopurine methyltransferase	Mercatopurine, thioguanine, azathioprine	Thiopurine toxicity and efficacy, risk of second cancers
UDP-glucuronosyl-transferase (UGT1A1)	Irinotecan, troglitazone, bilirubin	Irinotecan glucuronidation and toxicity, hyperbilirubinemia (Crigler-Najjar syndrome, Gilbert's syndrome)
UDP-glucuronosyl-transferase (UGT2B)	Opioids, morphine, naproxen, ibuprofen, epirubicin	Significance unknown

https://www.slideshare.net/DeepakKumar2053/polymorphism-affecting-drug-metabolism

As a result of genetic polymorphism

- Differences in related gene products
- Differences in the target of the drug
- Differences in drug metabolism can be reported

N-ACETYLTRANSFERASE

- Acetylation of aromatic amines, hydrazines the major route of biotransformation.
- Generally decreases water solubility
- Humans express two forms, NAT1; NAT2
- Cofactor is AcetylCoenzyme A
- Ethnic variation is seen
- Rapid and slow acetylators
- Various mutations result in decreased enzyme activity or stability
- Incidence of slow acetylators :70% in Middle Eastern populations; 50% in Caucasians; 25% in Asians
- Drug toxicities in slow acetylators: nerve damage from dapsone; bladder cancer in cigarette smokers due to increased levels of hydroxylamines
- NAT2 protein is the specific protein isoform that acetylates **isoniazid**.

SULFOTRANSFERASE

- Sulfotransferases are widely-distributed enzymes
- Cofactor is 3’-phosphoadenosine-5’- phosphosulfate (PAPS)
- Produce highly **water-soluble** sulfate esters, eliminated in urine, bile
- Xenobiotics & endogenous compounds are sulfated (phenols, catechols, amines, hydroxylamines)
- Sulfation is a high affinity, low capacity pathway, Glucuronidation is low affinity, high capacity
- Capacity limited by low PAPS levels
- **Acetaminophen** undergoes both sulfation and glucuronidation
- At low doses sulfation predominates while at high doses, glucuronidation predominates

METHYLTRANSFERASES

- Methylation is common, minor pathway which generally decreases water solubility
- Cofactor: S-adenosylmethionine (SAM)
- Methyl transfer to O, N, S, C
- Substrates include phenols, catechols, amines, heavy metals (Hg, As, Se)
- Several types of methyltransferases in human tissues
- Genetic polymorphism in **thiopurine** metabolism
- **high activity allele, increased toxicity**
- **low activity allele, decreased efficacy**

Thiopurine Methyltransferase

- The TPMT enzyme is responsible for the metabolism of chemotherapeutics in the class of thiopurine, such as mercaptopurine and azathioprine.

- Since the therapeutic range of thiopurines is narrow, administration of the same dose in all patients increases the risk of toxicity.

- Therefore, it is recommended that thiopurine doses be adjusted after determining the TPMT genotype before treatment.

Cateshol-O-Methyltransferase

- A functional variant in the catechol-O-methyltransferase (COMT) gene, the Val158Met ('val/met') polymorphism, this leads to 3-4 fold decre
- The metabolism of catholamine-derived drugs such as dopamine, levodopa, isoproterenol, methyldopa are affectedase in enzyme activity.

Glutathione-S-transferase (GST)

- Glutathione Conjugation is enormous array of substrates
- This enzyme catalyzes conjugation with glutathione
- Glutathione is tripeptide of glycine, cysteine, glutamic acid
- Genetic polymorphism

Class	Chromosome	Subunite	Allele	Enzyme activity
GSTM	1q13	GSTM1	Null	very low
GSTT	22q11	GSTT1	Null	very ow
GSTP	11q13	GSTP1	Ile105Val, Ala114Val	low

Polymorphism in GST

- A genetic polymorphism for GSTM1 has been identified, **resulting in a null allele**.
- Individuals who are homozygous for the **null allele** (i.e., those with low glutathione transferase activity due to complete deletion of the GSTM1 gene) appear to be at a moderately **increased risk for cigarette smoking-induced lung cancer, head and neck, and possibly bladder cancer.**

- *Depending on the ethnic group, 22 to 100% of the* population is homozygous for the GSTM1 null genotype, which results in a complete lack of GSTM1 activity in all tissues.
- *GSTM1 null allelle frequency is* 56.2% in healthy Turkish population.

- There is evidence that GSTM1 confers significant protection from breast cancer in individuals homozygous for a functional GSTM1 allele.

UDP-glucuronosyltransferase (UGT)

- Human UDP-glucuronosyltransferase (UGT) 1A1 is the enzyme that detoxifies neurotoxic bilirubin by conjugating it with glucuronic acid.
- UGT1A1 also plays a critical role in the detoxification and excretion of endogenous and exogenous lipophilic compounds mainly in the liver and gastrointestinal tract.
- Impaired or reduced UGT1A1 activity causes unconjugated hyperbilirubinemia (**Gilbert's syndrome and Crigler-Najjar syndrome**) and side effects of drug treatment such as SN-38 (active metabolite of the anticancer drug irinotecan)-induced toxicity.

BIOINFORMATIC

- Bioinformatics is the application of tools of computation and analysis to the capture and interpretation of biological data
- Bioinformatics is essential for management of data in modern biology and medicine

The attempt to use computer applications in biology, which started in the 1960s, has progressed in parallel with the technological development in both areas. The Bioinformatics branch that emerged as a result of this progress is one of the most popular academic and industrial sectors. The use of computers in molecular biology started with :

-graphic representation of three dimensional molecular structures,

-molecular sequences

-creation of three dimensional molecular structure databases.

Gene expression

- Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the product is a functional RNA.

Study areas

- Bioinformatics can generally be defined as the use of information technologies in the solution of biological problems. It is understood as the creation and operation of biological databases that support genomic sequences with its narrowest definition and the use of all existing computer applications in the solution of biological problems with its broadest definition.

- The impact of basic biological research on clinical applications and clinical medical information systems has become more decisive in the last 20 years and has led to the emergence of new generation of diagnostic and therapeutic modules.

- Although bioinformatics studies seem to be oriented towards basic scientific research, they will be indispensable for clinical informatics in the next ten years. For example, DNA sequencing information will be increasingly used in the medical forms of the diseases. Today, some insurance companies in the USA can request the current genetic screening test results when determining health insurance cost. Algorithms developed for bioinformatics research are expected to be integrated into clinical information systems very soon.

Toxicological Perspective

Prediction of possible toxic effects of drugs and chemicals, hazard detection and risk assessment

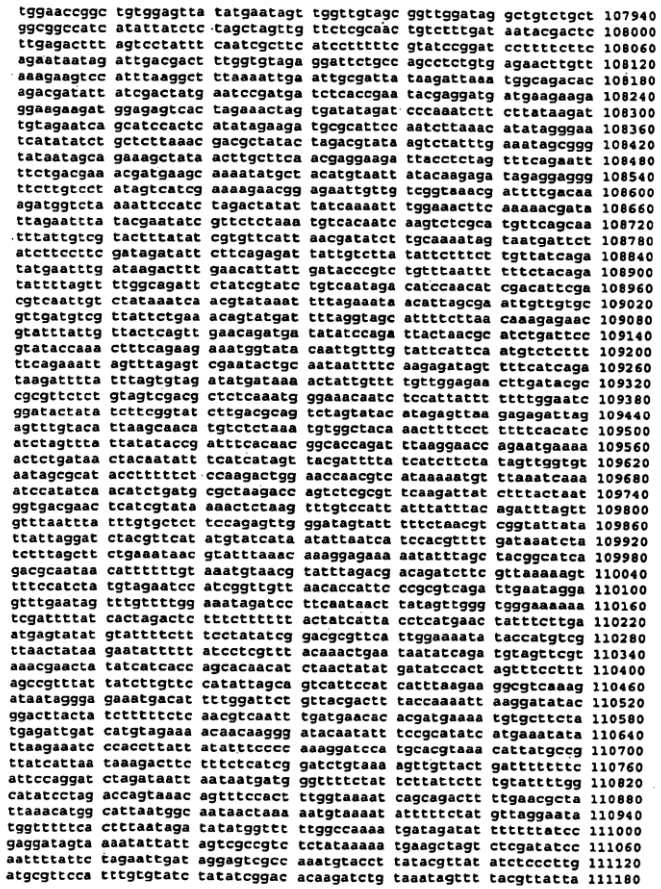
Safe dose determination

High-Throughput Screening
Phenotype Profiling platform

Mode of Action

Pharmaceutical Perspective

- It is applied in new rational drug designs.



Expressing a gene product to be harvested

Exemplary genes expressible by the vaccinia virus for the purpose of harvesting include human genes. An exemplary list of genes includes the list of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins University and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. Online Mendelian Inheritance in Man, OMIM™. Center for Medical Genetics, Johns Hopkins University (Baltimore, Md.) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, Md.), 1999. and those available in public databases, such as pubmed and genbank (see, e.g., (ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) These genes include, but are not limited to: 239f2h9, 3pk, 4ebp1, 4ebp2, al1, al2m1, al2m2, al2m3, al2m4, al5, alb, albg, alst, a2m, a2mr, a2mrap, aa, aaa, aaa, aabt, aac1, aac2, aact, aadac, aanat, aars, aas, aat, aavs1, abc1, abc2, abc3, abc7, abc8, abcr, abi1, abl1, abl2, abl1, abo, abp, abp1, abpa, abpx, abr, acaa, acac, acaca, acacb, acadl, acadm, acads, acadsb, acadv1, acat, acat1, acat2, acc, accb, accn1, accn2, accpn, ace1, ach, ache, achm1, achm2, achrb, achrd, achrg, acls,……

- The F3 gene also is conserved in the larger family of poxviruses, particularly among orthopoxviruses such as cowpox (nucleotides 58498-58647 of GenBank Accession No. X94355.2), rabbitpox (nucleotides 46969-47118 of GenBank Accession No. AY484669.1), camelpox (nucleotides 43331-43480 of GenBank Accession No. AY009089.1), ectromelia (nucleotides 51008-51157 of GenHank Accession No. AF012825.2), monkeypox (nucleotides 42515-42660 of GenBank Accession No. AF380138.1), and variola viruses (nucleotides 33100-33249 of GenBank Accession No. X69198.1).

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Analysis of preferred codon usage in the coronavirus N genes and their implications for genome evolution and vaccine design

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