

# GENETIC BASIS OF TOXICITY |

## Structure

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## 7.1 INTRODUCTION

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In the Unit 3, we learnt that the level of response (to toxicants and Adverse Drug Reactions 'or' ADRs to drugs) to a given dose of 'toxicant' or 'drug' (xenobiotics) may vary among different individuals of a population. Furthermore, some individuals (called 'sensitive individuals') in the population require a lower dose to show same level of response than that is required by many other individuals (called 'resistant individuals'). Other than this quantitative difference in the response, a small number of individuals in a population may also show the type of toxic responses which are qualitatively different from the responses shown by majority of the individuals (allergic response and idiosyncratic response). These aforementioned 'inter-human' (also known as 'inter-individual'/'intra-specific') variation in response to toxicants (or drugs) is caused by genetic polymorphism (existence of two or more alleles of genes) in the population, age and life stage of individual, gender, co-existing disease, lifestyle (smoking, alcohol, stress, exercise, etc.), nutritional status, etc. (Fig. 7.1). Polymorphism in the genes coding for proteins involved in xenobiotic 'transport' (membrane transporters, channels, carriers, etc.), 'metabolism' (xenobiotic metabolic enzymes), and 'target

molecules' (such as those with which a xenobiotic interacts to show effect, e.g. receptors, enzymes, channels, etc.) accounts for most of the observed inter-human variations in response to toxicants/drugs.

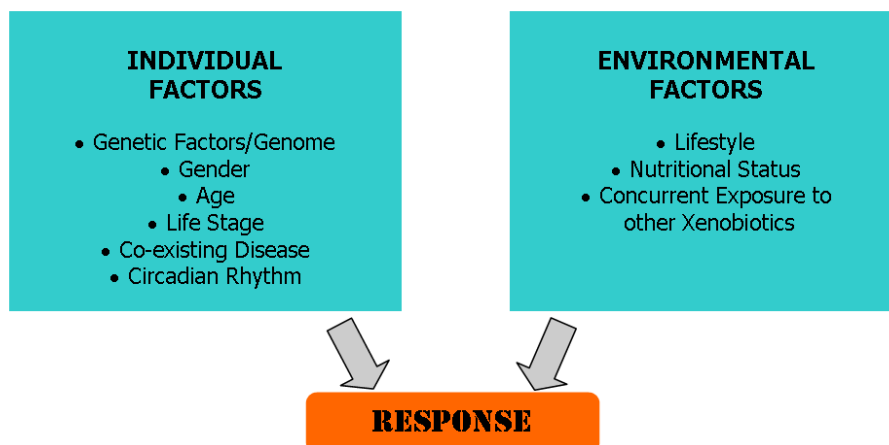


Fig. 7.1: Factors modifying response to toxicants/drugs.

In the Unit 5, we briefly discussed how polymorphism in the genes coding for xenobiotic metabolizing enzymes causes variation in toxic responses in a population. In the following section, we will learn more about it, and also, variation in toxic responses due to polymorphism in genes coding for xenobiotic transporters and receptors.

### Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ know the main reasons for inter-human variation in response to toxicants and drugs,
- ❖ know how genetic polymorphism can affect the outcome of toxic and drug response,
- ❖ know basics of molecular markers and their uses in the field of pharmacogenetics and pharmacogenomics.

## 7.2 GENETIC POLYMORPHISM AND VARIATION IN XENOBIOTIC RESPONSE

### 7.2.1 Variation in Response due to Polymorphism in Xenobiotic Metabolizing Enzymes

Polymorphism in the xenobiotic metabolism has been long recognized and a well-studied cause of inter-human variation in response to toxicants/drugs. Polymorphism or genetic variation in genes due to mutations may alter the

amino acid/s in the xenobiotic metabolizing enzymes, which may reduce or increase the activity of the enzyme molecule. In the simplest scenario (where a xenobiotic is metabolized by only one enzyme), it can be assumed that individuals in a population homozygous for the alleles producing defunct enzyme molecules will not be able to metabolize (or degrade) certain xenobiotics efficiently. Such individuals would accumulate xenobiotics in the blood and are at a risk to show toxic response. In other words, a dose inadequate to show toxic effects in most other individuals (harbouring normal alleles) is likely to cause toxicity in susceptible individuals.

We may categorize individuals in a population as; Poor Metabolizers (PMs), Intermediate Metabolizers (IMs), Extensive Metabolizers (EMs), and Ultra-rapid metabolizers (UMs). These individuals harbour 'no functional alleles', 'one functional/one dysfunctional allele', 'both functional alleles', and 'one or both alleles with gain in function', respectively. Table 1, lists a few polymorphic xenobiotic metabolic enzymes known to cause variation in response to toxicants/drugs in the human population.

Let us discuss this phenomenon with a few examples:

1. The isoform of CYP 450 i.e. CYP2C9 exists in more than 30 allelic forms. Two of the alleles (designated as CYP2C9\*2 and CYP2C9\*3) produce enzyme molecules in which substitution mutations results in reduced catalytic activity. The CYP2C9\*2 allele is more prevalent in Caucasians than in Asians. The drug warfarin, which has a low 'therapeutic index' is metabolized by CYP2C9. Individuals in a population homozygous for CYP2C9\*2 allele are prone to warfarin overdosing and resultant toxicity (such as bleeding). Therefore, a reduction in therapeutic dose is recommended in individuals who are PMs for warfarin.
2. The enzyme Aldehyde Dehydrogenase (ALDH) metabolizes aldehyde group in xenobiotics into carboxylic group. The isoform ALDH2 metabolizes simple aldehydes such as acetaldehyde. An allele of ALDH (ALDH2\*2) producing non-functional enzyme molecules (due to a point mutation) has been reported to be prevalent in individuals of Asian origin. Some individuals of this group also harbour an allele of Alcohol Dehydrogenase 'or' ADH (ADH1B\*2) which rapidly converts ethanol to acetaldehyde. Individuals harbouring both of these alleles rapidly convert ingested ethanol to acetaldehyde, but the acetaldehyde is slowly converted to acetate. Rapidly accumulating acetaldehyde in the blood stimulates release of catecholamines (nor-epinephrine, epinephrine) which causes immediate toxic effects including; nausea, headache, palpitations, abnormal blood pressure and heart beat, facial flushing.



3. The enzyme N-acetyltransferase (isoforms: NAT1 and NAT2) catalyzes acetylation of several drugs. Genetic polymorphism in NAT2 is known to cause toxicity by the drugs which are acetylated (or metabolized) by this enzyme. The antitubercular drug isoniazid is less efficiently metabolized and cleared from

### Therapeutic Index (TI)

This parameter is a measure of safety of drugs. It compares the dose which produces beneficial effects with the dose which produces toxic effects. It can be calculated as:

$$TI = LD_{50} / ED_{50}$$

Where LD 50 is the 'Lethal Dose' which can kill 50% of the experimental animals and ED 50 is the 'Effective Dose' which produces therapeutic effect in 50% of the experimental animals. These values can be obtained from the Quantal Dose Response Curves (see Unit 3).

It is evident from the formula that a safer drug should have higher 'TI' value. A drug with a low or narrow TI carries a risk of overdosing, and a person receiving such drugs should be closely monitored for any signs of drug toxicity.

the blood in individuals harbouring allele of NAT2 which slowly metabolizes the drug. This leads to a higher concentration of drug in the blood in these individuals compared to other who have normal alleles, putting the former group of individuals at risk of isoniazid toxicity.

**Table 7.1: A few xenobiotic metabolizing enzymes and their polymorphic isoforms.**

1. Cytochrome P450 (CYP)	5. UDP–glucuronosyltransferases (UGT)
CYP2D6	UGT1A1
CYP2C8	
CYP2C9	6. Sulphotransferases (SULT)
CYP2C19	SULT1A1
CYP2A6	SULT1A3
CYP2B6	SULT1C2
2. Aldehyde Dehydrogenases (ALDH)	SULT2A1
ALDH2	SULT2A3
	SULT2B1
3. Alcohol Dehydrogenases (ADH)	7. Thiopurine Methyltransferase
ADH2	TPMT
ADH3	8. N-acetyltransferase
4. Glutathione S-transferases (GST)	NAT2
GSTM1	NAT1
GSTT1	
GSTZ1	
GSTP1	

### Genetic Polymorphism

The 'human nuclear genome' in all the humans is consisted of 24 chromosomes (22 autosomes + X, Y sex chromosomes) and contains ~ 3 billion nucleotide pairs. The genomes of any two individual are ~ 99.6 % identical 'or' in other words only ~0.4% different. It is the difference of ~0.4% that makes each of as a unique individual. The differences (or genomic variations) in our genomes mainly occur in the form of: i) variations in a single nucleotide at several places in the chromosomes (Single Nucleotide Variations or SNVs), ii) insertion/deletion of few nucleotides and, iii) variations in the numbers of sets of 'unique repeating nucleotide sequence' in a stretch of chromosome (such as Copy Number Variations or CNVs). No two individuals have same pattern these genomic variations. Genomic variations make certain individuals overall prone to diseases/conditions such as hypertension, diabetes, obesity, etc. Genomic variations are also responsible for the observed differences in response to the drugs and toxicants among individuals of a population. If the nucleotide sequence at a particular location (locus) on a chromosome is variable and each of these variant (or alleles) occurs with a frequency of 1% or higher in a population in, those case the locus is said to be polymorphic i.e. harbouring more than one type nucleotide sequence. This is known as 'genetic polymorphism'. A polymorphic gene is the one which exists in more than one allelic forms (variants) with a frequency of 1% or higher in a population.

The most prevalent type of genomic variation that exists in our genome is SNVs. Since many of these variants exist with a frequency of 1% or higher, they are denoted as 'Single Nucleotide Polymorphisms (SNPs)'. SNPs are found throughout the human genome and the average density of SNP in the genome is about 1 (SNP) per 1000–1300 nucleotides. SNPs may lie in the 'coding regions' or the 'regulatory regions' of genes (such as promoters). SNPs occurring in the coding regions in the genes may not result in replacement of amino acid because of degeneracy of codons (synonymous substitution). Alternatively replacement of the original amino acids with the one with different physicochemical property often results in the loss or diminished protein function (non-synonymous substitution). SNPs in 'non-coding' but regulatory regions of genes (such as promoters) may result in alteration in the level of protein expression. SNPs lying in the other parts of non-coding genome (such as those considered 'junk DNA') does not cause any loss or gain of biological function in organisms.

### 7.2.2 Variation in Response due to Polymorphism in Xenobiotic Transporters

Cell membranes of all the cells in our body are embedded with several membrane transport proteins. These transporters enable hydrophilic endogenous molecules and xenobiotics to cross cell membranes (Table 2). Polymorphism in the genes coding for these transporters is another reason for the observed inter-human variation in response to atoxicant/drug. The polymorphism in transporters may cause inter-human differences in the ability to absorb xenobiotics, their distribution in the body, entry into the target cells, and excretion by the kidneys (tubular secretion) and liver (secretion of xenobiotics in bile) or other routes.

Xenobiotic transporters are integral membrane proteins, some of which use energy by hydrolyzing ATP to transport molecules across cell membrane.

Other transporters use ion gradient or, concentration gradient of xenobiotic across cell membrane to transfer xenobiotics from one-side-to other side of the cell membrane. Xenobiotic transporters can be grouped into three superfamilies, viz. ATP-Binding Cassette (ABC), Solute-Linked Carrier (SLC), and Solute Carrier Organic Anion (SLCO) superfamilies. The ABC transporters are 'primary active' transporters which use ATP to transport xenobiotics across cell membrane. The members of SLC superfamily are 'secondary active' transport proteins, whereas the mode of transport by SLCO is not well understood.

Let us discuss how polymorphism in the genes coding for transporters causes inter-human variation in the toxic responses using few examples:

1. Humans are exposed to the toxicant methyl-mercury (MeHg) by consuming fishes caught from contaminated water. MeHg is well absorbed from intestine and can cross blood-brain and placental barriers using various transporters. MeHg after being conjugated with glutathione is effluxed by cells of kidneys and liver in urine and bile respectively. MeHg can cause damage to foetal brain in mothers who have high level of toxicant in the blood due to consumption of contaminated fishes. Studies have found that women carrying a particular allele of transporter *ABCC1*, are likely to have higher MeHg burden in the body, and higher rate of MeHg transfer across placenta that may affect foetal neuronal development.
2. The drug 'Fenoterol' a  $\beta_2$ -adenoreceptor agonist is a bronchodilator and used to treat asthma. This drug also stimulates  $\beta_1$ -adenoreceptor present in the heart, causing cardiovascular toxicity in some patients. The drug is transported by OCT1 (coded by Gene *SLC22A1*). People with genetic deficiency of OCT1 when treated with fenoterol, achieve higher concentration of the drug in plasma, causing cardiac adverse effects. In another example, a particular allele of OCT1 transporter reduces the effectiveness of antidiabetic drug 'metformin' in some individuals. In these individuals, the drug is not efficiently absorbed in the intestine, and the transport of drug into liver as also affected.

**Table 7.2: Various transporters (genes) involved in transport of endogenous molecules across cell membrane.**

<b>ATP-Binding Cassette (ABC) Superfamily</b>	<b>Solute Carrier Organic Anion (SLCO) Superfamily</b>	<b>Solute-Linked Carrier (SLC) Superfamily</b>
<i>ABCA1</i> Cholesterol efflux onto HDL.	<i>SLCO1A2</i> Bile salts, organic anions and cations.	<i>SLC2A2</i> Facilitated glucose transporter.
<i>ABCB1</i> Peptides, steroids, bile salts.	<i>SLCO1B1</i> Bile salts, organic anions.	<i>SLC16A11</i> Transport of pyruvate.

<i>ABCC2</i> Organic anion efflux.	<i>SLCO1B3</i> Bilirubin bile acids, coproporphyrin I and III.	<i>SLC30A10</i> Manganese transport.
<i>ABCC3</i> Efflux of organic anions and glutathione conjugates and glucuronide.	<i>SLCO4A1</i> Taurocholate, T3, prostaglandin.	<i>SLC17A1</i> Sodium-dependent phosphate transporter 1, and renal transporter of uric acid.
<i>ABCB11</i> Bile salt transport.	<i>SLCO4C1</i> Thyroid hormones.	<i>SLC8A1</i> Sodium(Na <sup>+</sup> )- calcium(Ca <sup>2+</sup> ) exchanger 1.
<i>ABCB6</i> Iron transport.	<i>SLCO1C1</i> Steroid conjugates and thyroid hormones.	<i>SLC39A8</i> Zinc transport.
<i>ABCC4 &amp; ABCC5</i> Nucleoside transport.	<i>SLCO2A1</i> Eicosanoids and prostaglandins.	<i>SLC14A2</i> Urea transporter.
<i>ABCD1</i> Very-long-chain fatty acid (VLCFA) transport.	<i>SLC10A6</i> Bile acid and bile salt.	<i>SLC12A1</i> Sodium–potassium– chloride co-transporter.
<i>ABCG1</i> Cholesterol transport.	<i>SLC22A25</i> Organic anion transport.	<i>SLC6A13</i> GABA transporter.
<i>ABCB8</i> Peptide trafficking across membranes inside cell.	<i>SLCO1B7</i> Bile acid and bile salt transport and sodium- independent organic anion transport.	<i>SLC6A15</i> Branched-chain amino acids, particularly leucine, valine, isoleucine, and methionine.
<i>ABCG2</i> Efflux of Organic anion and sulphate conjugates, and biliary excretion.		<i>SLC7A9</i> Transport of cystine and neutral and dibasic amino acids.

### 7.2.3 Variation in Response due to Polymorphism in Xenobiotic Target Molecules

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Several xenobiotics initiate their toxic responses by interacting with body's protein molecules including: membrane and intracellular receptors; membrane transporters and channels; carrier proteins; enzymes and other proteins such as those involved in cytoskeleton (actin, tubulin, etc.). These target protein molecules may be coded by genes which exhibit genetic polymorphism. Thus, existence of more than one alternate form of 'protein target molecules' (coded by each allele of a polymorphic gene) in a population is also responsible for the observed inter-human variation in response to toxicants/drugs.

Let us discuss this with a few suitable examples:

The  $\beta$ 1-adrenergic receptor (ADRB) antagonists (such as propranolol, atenolol, metoprolol) are used to treat patients with essential hypertension. Studies have shown that in some individuals, an SNP in ADRB replaces 'arginine' at 389<sup>th</sup> position with 'glycine' which causes increase in response to the drugs. In another example, D3-dopamine receptor agonists (e.g. haloperidol) are used to treat schizophrenia. Patients in whom an SNP replaces 'serine' with 'glycine' at 9<sup>th</sup> position in D3-dopamine receptor are at risk of developing 'tardive dyskinesia' (repetitive involuntary body movements).

From the above discussions (sections 7.2.2–7.2.4), you may have realized how responses to toxicants and drugs are affected by the genetic makeup of individuals.

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#### SAQ 1

**State whether the following statements are true or false:**

- Genetic variations among individuals of a population, is the only cause for observed inter-human differences in responses to drugs and toxicants (True/False).
  - Existence of more than two alleles for xenobiotic metabolizing enzymes in a population may cause inter-human differences in responses to drugs and toxicants (True/False).
  - SNPs are the most common type of genetic variation in the human genome (True/False).
  - A nucleotide substitution in the gene, which causes replacement of original amino acid in the protein with another is called synonymous substitution (True/False).
-

## 7.3 MOLECULAR MARKERS

We have seen under the heading 'genetic polymorphism' (see box above) that– the variation 'or' polymorphism in DNA sequence is also found in those regions of the genome which have no known function. Such silent DNA variations (polymorphisms) do not cause any change in the function of organisms or appear as visible phenotype (phenotypically neutral). These polymorphisms however are useful as 'molecular markers', sometimes also referred as 'molecular genetic-markers' or 'DNA-markers'. A molecular marker is a polymorphic DNA-sequence with known physical location (locus) on a chromosome. Molecular markers are used in various fields such as, medicine, plant breeding, phylogenetic analysis, forensic investigations, etc. Since DNA segments in chromosomes located close to each other are inherited together, a molecular marker can thus be used as a tag for genes located in close vicinity, for which other details are not yet known or available. In this way, molecular markers can be used to monitor the inheritance of genes and alleles involved in a disease (useful in disease diagnosis and genetic counselling), or those genes that make persons susceptible to toxicants/ADRs (useful in preventing ADRs in patients with particular genotype). An ideal molecular marker should be highly polymorphic, co-dominant, and evenly distributed in the genome. Table 7.3 shows some of the widely used types of molecular markers.

**Table 7.3: A few types of molecular markers.**

<b>Types of molecular markers</b>
1. Restriction Fragment Length Polymorphism (RFLP)
2. Randomly amplified polymorphic DNA (RAPD)
3. Microsatellites
4. Amplified fragment length polymorphism (AFLP)
5. Single Nucleotide Polymorphism (SNP)

## 7.4 SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) AND PHARMACOGENETICS

*Pharmacogenetics*—a sub-discipline of pharmacology, studies effects of various alleles of one 'or' a few genes on inter-human variation in drug response (including ADRs). It is now known that the response to drugs is influenced by several genes (which may be polymorphic), and the observed variation in response is the outcome of complex interactions among the products (metabolic enzymes, receptors, transporters, channels, etc.) of these genes. A more holistic approach—*Pharmacogenomics* identifies influence of all

the genes (and their alleles) in the genome that may affect the response to drugs. Pharmacogenomics is a promising approach that can help in identifying the 'right dose' for a person based on his/her 'genetic makeup', in other words, a dose which is effective but free from any ADR. The corresponding sub-discipline in toxicology—*Toxicogenomics* studies influence of all the genes in a genome on the toxic response to a chemical.

Single Nucleotide Polymorphisms (SNPs) are the most common type of polymorphism found in the genome. SNP is the key molecular marker used in defining a person's genetic susceptibility to toxicants, chances to develop a disease and ADRs to drugs (in pharmacogenetic and pharmacogenomics approaches). SNPs located close to a gene (or allele) suspected to make individuals prone to exaggerated response to toxicants and ADRs, can be used as surrogate marker for the genes itself. Many SNPs directly mark a gene if the former are located in the coding regions. These features make SNPs a preferred molecular marker to draw a high-density molecular marker map of the genome.

SNPs are used as molecular markers in 'Genome Wide-Association Studies' (GWAS). The main aim in GWAS is to identify 'genetic variations' (such as SNPs) in the genome associated with a particular trait/disease/condition (such as extent of response to drugs and toxicants). In GWAS, genomes of several individuals are surveyed to look for SNPs associated with the disease and the results are compared with those of individuals without the disease under concern. Since the GWAS involves whole genome, the study identifies several SNPs that are associated with the disease or condition. To identify SNPs in the genome, SNP-arrays (a chip dotted with arrays of fragments of DNA used as probe) are used. The samples (DNA fragments from genome of individuals) are brought in contact with the chip and observed for hybridization with the probe.

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### SAQ 2

**Fill in the blanks with appropriate words:**

- a) Scientific approaches in which association SNPs and the disease under concern is studied are called..... .
- b) Sub-discipline of pharmacology where effect of single or a few gene variants is studied is called..... .

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## 7.5 SUMMARY

- There exists an inter-human variation in response to drugs and toxicants in a population. The most important cause of this variation is genetic polymorphism in the genes coding for xenobiotic metabolizing enzymes, xenobiotic transporters and xenobiotic target sites.

- More than one allele of xenobiotic metabolizing enzymes may exist in the population which may code for the enzyme molecules with reduced or enhanced enzymatic activity. This causes some individuals of the population to metabolize xenobiotics at a slower rate than others. The former group of individuals thus may have a higher burden of xenobiotic in the blood leading to exaggerated toxic response or Adverse Drug Reactions. Similarly, existence of more than one allele for xenobiotic transporters causes some individual to absorb more xenobiotics than others resulting in observed variation in response.
- SNPs are single nucleotide DNA variations at a particular locus in the genome. SNPs are the most commonly used molecular markers in the pharmacogenetics and pharmacogenomics approaches.

## 7.6 TERMINAL QUESTIONS

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1. What are the causes of inter-human variation in responses to xenobiotics in a population?
2. Discuss genetic polymorphism.

## 7.7 ANSWERS

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### Self Assessment Questions

1. a) False b) True c) True d) False
2. a) Genome Wide-Association Studies  
b) Pharmacogenetics

### Terminal Questions

1. Inter-human variation in response to xenobiotics is caused by two main variables i) genetic polymorphism in the population and ii) environmental factors: age and life stage of individual, gender, co-existing disease, lifestyle, nutritional status, etc. Polymorphism in the genes coding for proteins involved in xenobiotic transport, metabolism and xenobiotic target molecules, accounts for most of the observed inter-human variation in response to toxicants/drugs. Existence of more than one allelic form of these genes causes differences in absorption, metabolism and excretion of xenobiotics, and interaction with the target molecule among different individuals of the population. This results in the variation in toxic response.
2. Genetic polymorphism is the difference in the nucleotide sequence at a particular location (locus) on a chromosome which occurs with a frequency of 1% or higher in a population. The differences or genetic variations at various loci may be in the form of– i) variations in a single nucleotide (Single Nucleotide Variations or SNVs), ii) insertion/deletion of few nucleotides and, iii) variations in the numbers of sets of 'unique

repeating nucleotide sequence' in a stretch of chromosome (such as Copy Number Variations or CNVs). SNVs are the most common type of genetic variation, widely used as molecular markers in studies aimed to decipher association between molecular markers and a particular disease or a genetic condition.

## 7.8 FURTHER READINGS

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