Pharmacogenetics - Genetic Polymorphism in drug metabolism Cyt P450 in

Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response.

Pharmacogenomics refers to the general study of all of the many different genes that determine drug behavior.

Pharmacogenetics is the study of how genes affect the way people respond to drug therapy.

- Pharmacogenetics is an established discipline that studies the genetic basis of interindividual variability in the response to drug therapy, and allows for individualization of drug therapy.
- This genetic knowledge improves our ability to select or design the proper drug for individuals suffering from a disease with a varying range of molecular defects.

Example of Polymorphisms.

- Interindividual differences in response to drug therapy due to differences in acetylation of drugs is a well-studied example of genetic polymorphism.
- Patients' ability to metabolize certain drugs such as hydralazine, procainamide, and isoniazid can be categorized as either "fast acetylators", "normal acetylators" or "slow acetylators. Acetylation status is dependent on the patient's genetic composition, which determines the activity of the acetylation enzyme N-acetyltransferase. Acetylation status determines whether a patient is dosed with a correspondingly higher or lower dose compared to "normal acetylators".
- The goal of pharmacogenetics is to individualize drug therapy to a person's unique genetic makeup

• The environment, diet, age, lifestyle and state of health can influence a person's response to medicine.

• Pharmacogenomics involves study of the role of genes and their genetic variations (DNA, RNA level) in the molecular basis of disease.

• The (CYPs) are superfamily of haemoprotein enzymes found on the membrane of endoplasmic reticulum. They are responsible for catalyzing the metabolism of large number of endogenous and exogenous compounds.

• CYPs are also known as mixed function oxidases and mono-oxygenases as metabolism of a substrate by a CYP consumes one molecule of molecular oxygen and produces an oxidized substrate and another molecule of oxygen appears in water as byproduct.

*Isozyme (isoenzyme) one of the multiple forms in which an enzyme may exist in an organism or in different species, the various forms differing chemically, physically or immunologically, but catalyzing the same reaction.

- These enzymes are responsible for biotransformation of drugs and are body's defense against xenobiotics along with P-glycoprotein.
- Cytochrome P450 isoenzymes are predominantly present in liver but are also found in intestine, lungs, kidneys, brain, etc.
- Cytochrome P450 isoenzymes are designated by the letters e.g. CYP2D6, "CYP followed by an Arabic numeral, a letter and another Arabic numeral (italics). 'P' in cytochrome P450 stands for 'pigment'.
- Each enzyme is termed as isoform since each is derived from a different gene. These isoforms have a spectrophotometric absorption peak at or near 450nm when bound and reduced by carbon monoxide.

Families- proteins with at least 40% amino acid sequence homology. In humans upto 21 families have been described e.g. CYP2, CYP3.

Subfamilies- members of the same family must have at least 55% amino acid sequence homology e.g. CYP2D, CYP3A.

Individual genes- they are denoted by Arabic numeral (italics), there are 50 or so genes important in man e.g. CYP2D6, CYP3A4.

- In the humans upto 21 families, 20 subfamilies and 57 genes have been described.

→ CYP2D6

→ CYP1A2

→ Cyp2C9

→ CYP2C19

CYP2D6:

- Is a large isozyme family that affects metabolism of many drugs.
- is highly polymorphic.
- Drugs whose metabolism is affected by CYP D6 polymorphism
  - Tricyclic antidepressants
  - Clomipramine
  - Desipramine
  - Imipramine

- Genetic polymorphism of CYP 2D6 was first investigated with debrisoquine.
- Poor metabolizers often carry two nonfunctional alleles of this gene, resulting in reduced drug clearance.
- Poor CYP 2D6 metabolizers have increased

plasma concentrations of tricyclic antidepressants when given recommended doses of the drug.

CYP1A2:

- CYP1A2, metabolizes 5% of randomly selected drugs.
- Fluvoxamine is a substrate and potent inhibitor of CYP1A2, causing important interactions with drugs such as amitriptyline, clomipramine, imipramine, clozapine, and theophylline that are partly metabolized by this cytochrome P-450 enzyme

CYP2C9:

Polymorphism of CYP2C9 is associated with decreased enzyme activity.

Eg: Anticoagulant- warfarin

- These patients had an increase incidence of major

and minor hemorrhage.
And therefore requires low dose of warfarin.

CYP 2C19:

Frequency of Polymorphism 3-6% (whites)
8-23% (Asians)

Ex: Omeprazole

Higher cure rate when gives ē clarithromycin

Ex: Diazepam

Prolonged sedation.

It is involved in metabolism of several important groups of drugs including PPI and antiepileptics and is involved in metabolism of xenobiotics.

Ex:- CYP 2 D6

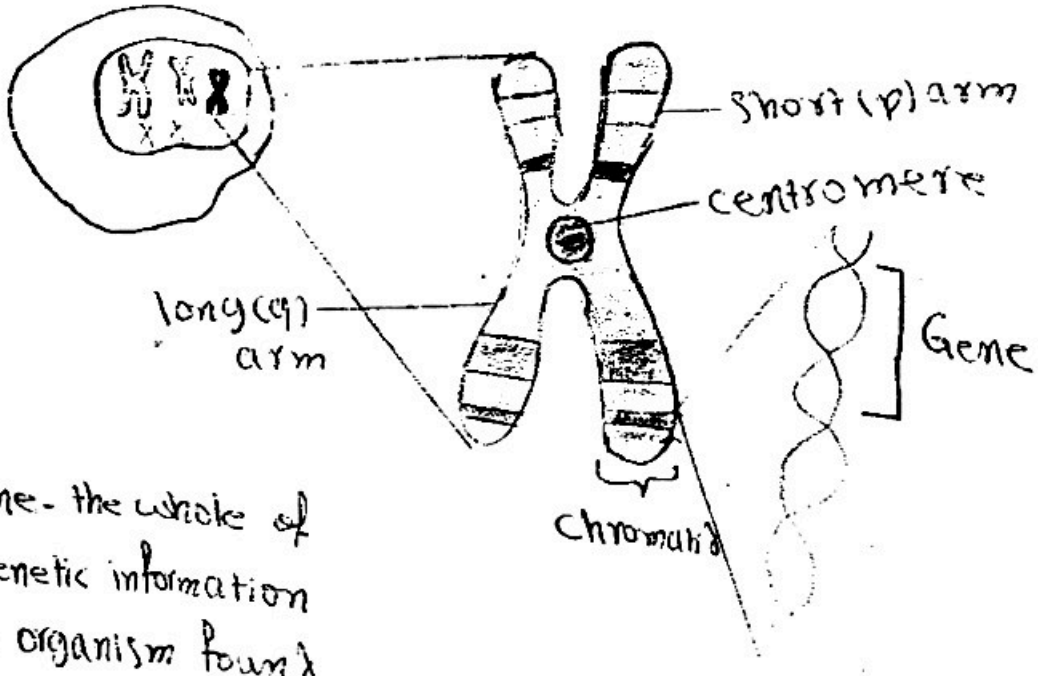
- Polymorphic-O-demethylation of codeine is

one clinical important when this drug is given as analgesic.

About 10% codeine is demethylated by CYP 2D6 to morphine and this conversion is deficient in poor metabolizers → poor metabolizers therefore experience no analgesic effect of drug.

- Genetic polymorphism:

The existence together of many forms of DNA sequences at a locus within the population.



Genome - the whole of the genetic information of an organism found in the nucleus of eukaryotes.

. A locus, is the specific location or position of a gene, DNA sequence, on a chromosome.

. An allele is one of a pair of genes that appear at a particular location on a particular chromosome and control the same characteristic, such as blood type