Pharmacogenomics

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- **Pharmacogenomics** (or pharmacogenetics)
- Is the study of the genetic variations that cause differences in drug response among individuals or populations.

- Some patients respond to certain drugs with greater than usual sensitivity to standard doses.
- Such increased sensitivity is due to a very small genetic modification which result in decreased activity of a particular enzyme responsible for eliminating that drug.

The dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients because of individual differences in drug distribution and rates of drug metabolism and elimination.

These differences are determined by :

- Genetic factors
- Non genetic variables (age, sex, liver size, liver function, circadian rhythm, body temperature, nutritional and environmental factors such as concomitant exposure to inducers or inhibitors of drug metabolism.

Genetic Factors

- The defects are apparently transmitted as autosomal recessive traits and may be expressed at any one of the multiple metabolic transformations that a chemical might undergo
- Genetic factors that influence enzyme levels account for some of these differences.

Examples of Pharmacogenetic Differences

1. Succinylcholine is not completely metabolized in persons with genetically determined defects in pseudocholinesterase, while it completely metabolized in persons with normally functioning pseudocholinesterase.

2. The acetylation of isoniazid

Acetylation is genetically regulated.

1. The fast acetylators
2. Slow acetylators
   - In slow acetylator phenotype ,the defect is the synthesis of less of the enzyme rather than of an abnormal form of it.
   - Slow acetylators (excrete more of the parent compound). So, Severely depressed renal function results in accumulation of the drug

3. Warfarin

- Genetic factors make an important individual variation on Pharmacokinetic & on Pharmacodynamic of warfarin

- **On Pharmacokinetic (The oxidation of warfarin)**
  - Several cytochromes p450 each of which shows genetic polymorphism leading to individual variation in levels of activity contribute to oxidative metabolism of warfarin
  - The most important of these is CYP2C9, the genetic variation on CYP2C9 result in decrease enzyme activity ,so need decreased in warfarin dose.

- **On Pharmacodynamic of warfarin**
  - Due to abnormal vitamin K epoxide reductase (the enzyme that is inhibited by warfarin**)**
  - This effect on mechanism of action of warfarin