Pharmacogenomics

Chapter 8
Introduction

- Heterogenicity in genetic makeup contributes to many variations in pharmacokinetics.
- Various factors contribute to specific observable pharmacodynamic differences.
- Majority of drugs are metabolized through the CYP450 enzyme system.
- Differences between poor metabolizers and extensive metabolizers impact provider management.
- Applying pharmacogenomics to clinical practice.
What is pharmacogenomics?

- **Pharmacogenomics** is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression with a drug's efficacy or toxicity.

- In other words, drugs and drug combinations are optimized for each individual's unique genetic makeup.
Physiology Review

- Although humans share 99.9% of DNA sequence, the < 0.1% differences is about 3 million nucleotides.
- Of the 0.1% difference, over 80% will be single nucleotide polymorphisms (SNPs). A SNP is a single base substitution of one nucleotide with another
- An example of a SNP is individual "A" has a sequence GAACCT while individual "B" has sequence GAGCCT, the polymorphism is a A/G.
Review: CYP 450

- CYP enzymes involved in about 75% of drug metabolism and bioactivation in the liver.
- Some CYPs metabolize only one (or a very few) drug, while others may metabolize multiple drugs.
- Genes provide the coding for CYP enzymes, and the enzymes themselves, are designated with the abbreviation CYP, followed by an Arabic numeral indicating the gene family, a capital letter indicating the subfamily, and another numeral for the individual gene. For example, CYP2E1 is the gene that encodes the enzyme CYP2E1 – one of the enzymes involved in acetaminophen metabolism.
Role of P-Glycoprotein (P-gp)

- **P-gp**: membrane bound transport system responsible for drug transport across cell membranes.
- **P-gp**, an efflux pump expressed along the gastrointestinal tract, limits the permeability of many drugs and thus affects their absorption and bioavailability.
- A number of drugs inhibit or activate both CYP450 and P-gp at the same time (i.e. grapefruit juice)
Pharmacodynamic Differences

- How does a person’s genetic make up affect CYP enzyme function and pharmacodynamic differences?

- What other factors besides genetic coding contribute to pharmacodynamic differences?
CYP450 In Clinical Practice

- Clinical knowledge of substrates, inhibitors, and inducers for each CYP450 family assists clinicians in predicting potential drug-drug interactions.
  - CYP3A subfamily responsible for over 50% of drug metabolism
- Race, gender, environmental factors, and drugs may alter the gene expression of individual CYP450 families and subfamilies.
  - 40% of Asians display drug polymorphism
- There is no specific clinical test to estimate sensitivity or activity of CYP450.
Inhibitors vs. Inducers of CYP450

- What are the clinical implications when substrates inhibit CYP450 enzymes?
  - An inhibitor may decrease the metabolism of substrates and generally lead to an *increased* drug effect.

- What are the clinical implications when substrates induce CYP450 enzymes?
  - An inducer may increase the metabolism of substrates and generally lead to a *decreased* drug effect.
CYP450 In Clinical Practice

- CYP families 1-3 have the least affinity for substrates and have the widest genetic variability.
  - They are responsible for 78-80% of phase I metabolism-drug interactions in clinically used drugs.
  - Variations or polymorphisms in genetic codes for these CYP enzymes have tremendous clinical importance.
Variations in Phenotypes Affects Speed of Metabolism

- **Poor metabolizers:** homozygous for lack of
  - of a working enzyme
- **Intermediate metabolizers:**
  - Are heterogenous for one working wild-type allele and one mutant-allele
- **Extensive metabolizers:** homozygous
  - Have two normally functioning alleles
- **Ultra-rapid metabolizers:** heterozygous for
  - more than one functioning copy of a certain enzyme.
Variation of Alleles

- **Slow metabolizers:** homozygous, have 2 copies of alleles that cause slow metabolism because they lack the working enzymes.

- **Fast metabolizers:** homozygous, have 2 copies of alleles that cause fast metabolism because they have working enzymes; heterozygous one allele may have more than one copy for making working enzymes.
Clinical Implications of Pharmacogenomics

- Pharmacogenetic testing before prescribing
  - Cetuximab
  - Trastuzumab
  - Maraviroc
  - dasatinib
- **Warfarin:**
  - Variants in VORC1 may lead to resistance
  - Label updated by the FDA to include recommended starting doses depending on the VKORC polymorphism profile

- **Carbamazepine:**
  - FDA labeled recommending testing for the *HLA-B*1502 allele in patients with Asian ancestry before initiating carbamazepine therapy due to high risk of developing carbamazepine-induced Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis