



Pharmacogenomics principles and concepts

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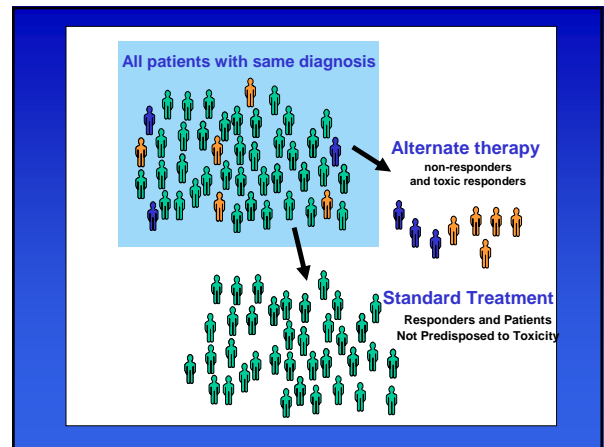
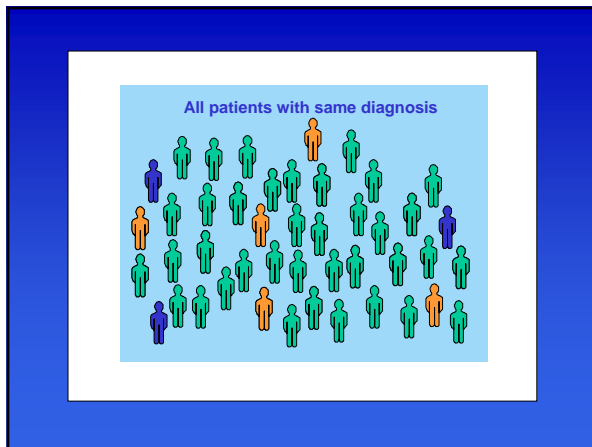
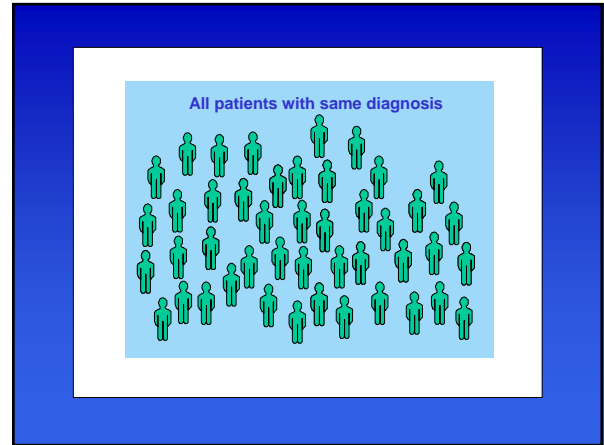
Objectives:

1. Describe and define pharmacogenomic concepts and taxonomy
2. Identify the key advances that have been made in the Human Genome Project
3. Describe pharmacogenomic principles and the effect on pharmacokinetics and dynamics

**“A surgeon who uses the wrong side of the scalpel cuts her own fingers and not the patient;
if the same applied to drugs they would have been investigated very carefully a long time ago”**

Rudolph Bucheim
Beitrag zur Arzneimittellehre, 1849

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The clinical problem

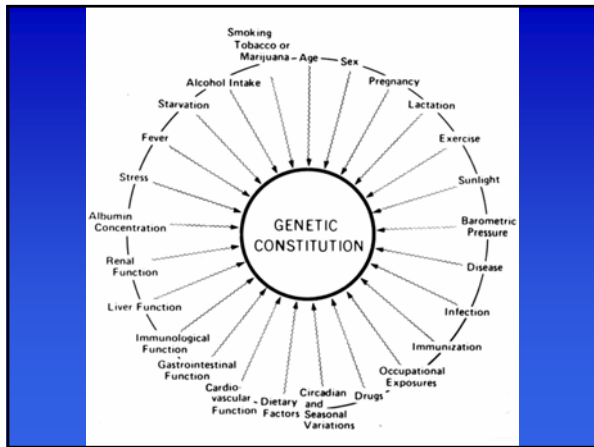
- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

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With choice comes decision

Pharmacokinetics
What the body does to the drug

Pharmacodynamics
What the drug does to the body



What Exactly is Genetics?

Genetics is the study of heredity...

...and of variation between individuals

Pharmacogenetics vs Pharmacogenomics

- Pharmacogenetics
 - The effect of genetic variation on drug response (disposition, safety, tolerability, and efficacy)
- Pharmacogenomics
 - The application of genome science (genomics) to the study of human variability in drug response

<http://www.fda.gov/downloads/Drugs/ScienceResearch/Research/Pharmacogenetics/ucm116702.pdf>

The History of Pharmacogenetics

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1866 – Gregor Mendel establishes rules of heredity

2003 – FDA issues draft guidelines for submission of pharmacogenetic data with NDAs

Source: U.S. Nature Reviews Genetics 3, 603-676 (September 2004)

Chromosomes

- Every human cell with the exception of the gametes contains 23 pairs of chromosomes
- code for all the proteins in every cell
 - Resides in the cell nucleus
- Each chromosome contains one DNA molecule

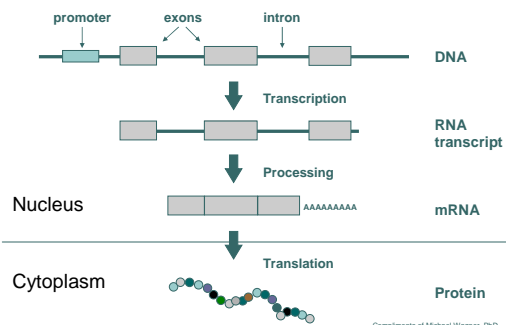


http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm116702.pdf

DNA

- DNA building blocks = 4 nucleotide bases
 - A (adenine)
 - G (guanine)
 - T (thymine)
 - C (cytosine)
- Single strand
 - sugar-phosphate backbone
- Double strand
 - Double helix
 - Bound by hydrogen bonds
 - Always A-T; C-G

Anatomy and Expression of a Gene



Compliments of Michael Wagner, PhD

SNP (pronounced snip) single nucleotide polymorphism

- Variation in DNA sequence
- >1% population = genetic polymorphism
- Variations
 - Cause of human differences
- Alter protein synthesis and mRNA function

PharmGenEd Module 1: University of California at San Diego

SNP's and Human Variation

- | | |
|---------------------------------|----------------------------------|
| ○ ...CCATTGACT | ○ ...GAAAGCCCC |
| ○ CCGTTGACT | ○ GAAGGCCCC |
| ● CCA = proline | ● AGC = serine |
| ● CCG = proline | ● GGC = glycine |
| ○ No AA change = synonymous SNP | ○ AA change = non-synonymous SNP |

Other Polymorphisms -- Insertions

- Insertion
 - UGT1A1
 - Nucleotide change = Insert T and A repeat
 - (TA)₆>(TA)₇
 - ↓ function; ↓ glucuronidation
 - Gilbert's syndrome, drug toxicity

Oncogene (2003) 22, 6621-6628

Other Polymorphisms – Deletion and Duplication

- Deletion (see diagram a)
 - CYP2D6
 - Delete several nucleotide base pairs
 - Loss of function; decreased metabolism
 - Phenotype = Poor metabolizer
- Copy Number Variation (see diagram b)
 - CYP2D6
 - Increased copies of CYP2D6 gene
 - Phenotype = Ultra-extensive metabolizer

Nature Reviews Drug Discovery 3, 749-761 (September 2004)



Allele

- Alternative forms at a genetic locus on one chromosome
- Most loci – humans have 2 chromosomes which carry the same or 2 different alleles
- One of several variants of a gene
 - Usually specific site within a gene



Heterozygous vs Homozygous

- Homozygous = two of the exact same alleles
 - Example CYP2C19*1/*1 (2 *1 alleles)
- Heterozygous = two different alleles
 - Example CYP2C19*2/*3 (one *2 and one *3 allele)



Human Genome Project

- Genomics: study of genes and their function
- Human Genome Project (HGP)
 - Began in 1990
 - Coordinated by Dept of Energy & NIH
 - Working draft published (90% complete) Science & Nature Feb 2001



Human Genome Project

- HGP Goals:
 1. Determine the sequence of the 3 billion DNA nucleotides
 2. Chart variations among the sequences
 3. Label functions of the ~ 30,000 human genes
 4. Address ethical, legal, and social issues



Genetic polymorphisms of drug disposition and drug targets

Growing list of published examples

- > 35 Drug metabolizing enzymes
- > 12 Drug transporters
- > 40 Drug targets

McLeod & Evans, *Annu Rev Pharmacol Tox*, 2001
Evans & McLeod, *N Engl J Med*, 2003
Weinshilboum, *N Engl J Med*, 2003

Clopidogrel Clinical Pharmacology

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Ellis KJ et al. Pharmacogenomics. 2009; (in press).

Clopidogrel PGx – PK/PD

Clopidogrel
↓ **CYP2C19*1 (wild-type)**
Active metabolite
|
Platelet Function

Clopidogrel PGx - PK

Clopidogrel
↓ **CYP2C19*2 or *3**
Active metabolite
PK (higher clopidogrel exposure)

Kim et al. CP&T. 2008;84:236-42.

Clopidogrel PGx - PD

Clopidogrel
↓ **CYP2C19*2 or *3**
Active metabolite
|
Platelet Function
PD (less inhibition of aggregation)
Korean HVTs

Kim et al. CP&T. 2008;84:236-42.

Clopidogrel PGx – PK/PD

Clopidogrel
↓ **CYP2C19*2 or *3**
Active metabolite
|
Platelet Function

Mega et al. NEJM. 2009;360:354-62.

Clopidogrel PGx – Clinical Outcome

TRITON-TIMI 38, PGx Sub-Analysis (N=1459)

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Mega et al. NEJM. 2009;360:354-62.

Pharmacogenomic examples-2009

- *bcr/abl* or 9:22 translocation—imatinib mesylate
- HER2-*neu*—trastuzumab
- C-kit mutations—imatinib mesylate
- Epidermal growth factor receptor mutations—gefitinib
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine
- UGT1A1-irinotecan
- CYP2C9/VKORC1-warfarin
- CYP2C19-clopidogrel
- HLA-B*5701-abacavir
- HLA-B*1502-carbamazepine
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen

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PharmGKB (www.pharmgkb.org)

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Resources for Pharmacogenomic Information

- PharmGKB (www.pharmgkb.org)
- NLM (<http://ghr.nlm.nih.gov/>)
- JAMA 3 article series 2009
 - How to use an article about genetic association
 - Author John Attia
 - Great appendix of terms
- FDA
 - <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm116702.pdf>
 - <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>

Goal of Pharmacogenomics

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<http://dna-assessmentonline.com/images/00000113.jpg>
http://www.hanpen.com/combobios_people/mixedly.html
<http://www.160172525.com>

