Clinical Chemistry
Trainee Council

PEARLS OF LABORATORY MEDICINE

Introduction to Pharmacogenetics

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Outline

- The concept of Pharmacogenetics
  - Prevalence of adverse drug reactions
  - Limited drug efficacy
  - Benefits of pharmacogenetics-based dosing
- Influence of genetics on drug metabolism and action
  - Pharmacokinetics and pharmacodynamics (PK/PD)
  - Common PK/PD genes implicated in pharmacogenetics
- Pharmacogenetics in drug labels
- Testing methodologies in Pharmacogenetics
- Pharmacogenetics Resources

Adverse Drug Reactions

- 3-11% hospital admissions are attributed to Adverse Drug Reactions (ADR)
- 2 Million ADRs/year
- 110,000 fatal ADRs/year
- 4-6th leading cause of death in the U.S.

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200-5.

Adverse Drug Reactions

- Examples of drugs that were withdrawn due to ADR (incomplete list)
  - Thalidomide
  - Phenformin, buformin
  - Fen-phen
  - Troglitazone
  - Cerivastatin
  - Rofecoxib
  - Propoxyphene
- Targeted drug administration/dosing based on individual genetics would help avoid these withdrawals?

Limited Drug Efficacy

- Response rates of patients to various drugs
  - Cancer drugs 25%
  - Depression drugs (SSRIs) 62%
  - Asthma drugs 60%
  - Diabetes drugs 57%
  - Migraine drugs 50-52%

Spear BB, Heath-Chiozzi M, Huff J. Clinical Application of Pharmacogenetics. Trends in Molecular Medicine. 2001;7(5):201-4.

Pharmacogenetics/Pharmacogenomics

- Pharmacogenetics/Pharmacogenomics
  - examines *variations in genes* that *dictate drug response*
  - explores the ways these variations can be used to *predict* whether an individual patient will have a good, or a bad response to a drug, or no response at all
  - Help determine what dosage should be given
  - Right patient, right drug, right time, right dose
  - Single Nucleotide Polymorphisms (SNPs), insertions, deletions, duplications and translocations

Genotype and Haplotype

- Genotype: the specific allele inherited at a locus
  - eg. *CYP2C9* (cytochrome P450 2C9) *c.430C>T* or *c.430C* and *c.430T*
- Haplotype: the collective genotype of a number of closely linked loci on a chromosome
  - eg. *VKORC1* (Vitamin K epoxide reductase complex subunit 1) *c.381C, c.861C, c.2653G, c.3673A, c.5808T, c.6009C, c.6484T, c.6853C, c.7566T, c.9041G*; or *H1*

Benefits of Pharmacogenetics-based Dosing

- Achieve optimal dose more quickly, avoid trial and error
- Avoid drugs that patients would suffer severe side effects from or would not benefit from
- Stratify patients for clinical trial, only include patients who are likely to respond
- Improve patient adherence to drug regimen

Companion Diagnostics

Companion Diagnostic Target	Drug
HER-2/NEU	Trastuzumab, pertuzumab
EGFR	Cetuximab, panitumumab
c-Kit	imatinib mesylate
ALK	crizotinib
BRAF V600	vemurafenib
KRAS	cetuximab

Complete list available at FDA website:
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

Pharmacokinetics/Pharmacodynamics

- Pharmacokinetics (PK): what the body does to the drug
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - Drug transporters, metabolizing enzymes
- Pharmacodynamics (PD): what the drug does to the body
  - Drug targets, downstream molecules involved in mechanism of action

Common PK/PD Genes Implicated in PGX

- Phase I metabolizing enzyme genes:
  - Introduce or expose reactive or polar groups
  - Oxidation, reduction and hydrolysis enzymes
  - CYP450s: superfamily of monooxygenases
  - Esterases, hydrolases
  - May convert inactive prodrugs (e.g., *CYP2C19* for clopidogrel) to active metabolites
  - May convert active drugs (e.g., *CYP2C9* for warfarin) to inactive metabolites

Common PK/PD Genes Implicated in PGX

- Phase II metabolizing enzyme genes:
  - Encoding Conjugation enzymes
  - Glucuronic acid, sulfate, glutathione, methyl etc.
  - *UGT1A1* for irinotecan and *TPMT* for azathioprine and 6-mercaptopurine
- Transporter genes: *ABCB1* (*MDR1,* encoding P-gp)
- Other enzyme genes: *G6PD*, *AChE*
- Receptors/target genes: *VKORC1* for warfarin

Pharmacogenetics in Drug Labels (incomplete list)

Drug	Indication	PGx genes
imatinib	C-Kit+ gastrointestinal stromal tumor	*C-Kit+*
tositumomab	CD20+ non-Hodgkin's lymphoma	*CD20 antigen*
lenalidomide	Transfusion-dependent anemia in myelodysplastic syndrome	*Deletion of ch5q*
Cetuximab, panitumumab	Colorectal cancer	*EGFR, KRAS*
fulvestrant	Metastatic breast cancer	*Estrogen receptor*
Trastuzumab,lapatinib	Breast cancer	*HER2*
dasatinib	Acute lymphoblastic leukemia	*Philadelphia chromosome*
tretinoin	Acute promyelocytic leukemia	*PML/RARa*

- Pharmacogenomic Biomarkers in Drug Labels (complete list): http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Pharmacogenetics in Drug Labels (incomplete list)

Drug	Adverse effect	PGx genes
clopidogrel	thrombotic events	*CYP2C19*
warfarin	bleeding	*CYP2C9, VKORC1*
atomoxetine	toxicity	*CYP2D6*
capecitabine	toxicity	*DPD*
carbamazepine	Severe dermatologic reactions	*HLA-B*1502*
Abacavir	Hypersensitivity reactions	*HLA-B*5701*
Mercaptopurine, azathioprine, thioguanine	Myelotoxicity	*TPMT*
Irinotecan	Neutropenia	*UGT1A1*

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Testing methodologies in Pharmacogenetics

- By phenotyping: metabolic probe drug , western blot or immunohistochemistry
- FISH
- PCR, mutation-specific endonuclease and electrophoresis
- PCR and allele-specific hybridization (microarray chip or bead)
- Taqman probe screening (FRET)
- Relief of quenching/FRET without PCR
- Relief of quenching/FRET in the process of PCR (allele-specific ligation, RT-PCR)
- Direct sequencing (classical Sanger's method), pyrosequencing or next-gen sequencing
- Mass spectrometry (MALDI-TOF) after PCR

Pharmacogenetics Resources

- A Science Primer--National Center for Biotechnology Information http://www.ncbi.nlm.nih.gov/About/primer/pharm.html
- PharmGKB: The Pharmacogenetics and the Pharmacogenomics Knowledge Base http://www.pharmgkb.org
- NIH NIGMS Pharmacogenomics Research Network http://snp.cshl.org
- The SNP consortium http://snp.cshl.org
  - dbSNP database-- National Center for Biotechnology Information (NCBI) http://www.ncbi.nlm.nih.gov/snp
- CYP allele nomenclature database http://www.cypalleles.ki.se

References

- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200-5.
- Spear BB, Heath-Chiozzi M, Huff J. Clinical Application of Pharmacogenetics. Trends Mol Med 2001;7:201-4.
- Patterson SD, Cohen N, Karnoub M, Truter SL, Emison E, Khambata-Ford S, et al. Prospective-retrospective biomarker analysis for regulatory consideration: white paper from the industry pharmacogenomics working group. Pharmacogenomics 2011;12:939-51.
- Evans WE and Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999;286:487-91.

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