Pharmacogenomics: Implications for Pediatric Nurses

Nicole L. Mollenkopf, PharmD, MBA, BCPS
Assistant Professor, Johns Hopkins School of Nursing
Objectives

1. Define pharmacogenomics
2. Discuss genetic variations that have the potential to influence safe and effective medication use
3. Review resources available to access curated pharmacogenomics information
If it were not for the great variability among individuals, medicine might be a science not an art.

- William Osler, 1892
“One Size Does Not Fit All”

“Personalized Approach”

Without Personalized Medicine:
Some Benefit, Some Do Not

- Patients
  - Therapy
    - Benefit
    - No benefit
    - Adverse effects

With Personalized Medicine:
Each Patient Receives the Right Medicine For Them

- Patients
  - Biomarker Diagnostics
  - Therapy
    - Each Patient Benefits From Individualized Treatment

Personalized medicine is “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease.”

— National Institutes of Health, 2015
Promises of Personalized Medicine

- DIAGNOSING faster
- TARGETING right medicine to right patient
- PREVENTING complications and side effects
- IMPROVING outcomes for patients

Terminology

► Pharmacogenetics
  • Study of inherited differences (variations) in single gene and variability in drug disposition, response and toxicity

► Pharmacogenomics
  • Study of inherited differences in a large collection of genes (up to entire genome) and variability in drug disposition, response and toxicity
Human Genome

- Underpinning to every human’s individuality
- Different for each individual (except identical twins)
  - Consists of approximately 3 billion base pairs
  - 99.9% of which are the same among all humans
  - 0.1% variation among individuals
- Human genome sequencing project completed in early 2000’s
- Since then...
Fundamentals

- Genome
- Chromosome
- Gene
- Nucleotide (A, C, T, G)

Genetic Variation

Difference in DNA sequence compared to reference sequence

- Polymorphism
  - Variant that is common, often defined as 1% or more in population

- Mutation
  - Variant that is rare, defined as less than 1% in population
Types of Genetic Variants

- Single nucleotide polymorphism (SNPs)
- Insertion or deletion
- Variable number of tandem repeats
- Copy number variation
- Other
Other Important Definitions

- **Allele**
  - Wild-type
  - Variant allele

- **Genotype**
  - Homozygous
  - Heterozygous

- **Phenotype**
Clinical Pharmacogenomics

Drug Metabolizing Enzymes

Drug Transporters

Drug Targets

Pharmacokinetics

Pharmacodynamics

Variability in Efficacy or Toxicity

Pharmacokinetics: ADME

Fig. 4-1. **The four basic pharmacokinetic processes.** Dotted lines represent membranes that must be crossed as drugs move throughout the body.
Drug Metabolism

- Phase 1 enzymes
  - CYP1, CYP2, CYP3
  - Primarily in liver

- Phase 2 enzymes
  - Examples: UGT1A1, TPMT
  - Conjugation reactions with sulfuric acid, glucuronic acid, etc.
  - Typically diminish elimination increasing risk for toxicity

- Naming
  - Wild-type allele is the *1 (e.g., CYP2D6*1)
  - SNPs are then sequentially numbered as identified (e.g., CYP2D6*2, CYP2D6*3)
Genetic variants in drug metabolizing enzyme genes may **decrease** enzyme function

- Decreased enzyme activity
- Decreased affinity of enzyme for substrate (drug)
- Result in inactive (nonfunctional) enzyme
Genetic variants may result in *multiple copies* of the gene (much less common)

- Increased amount of enzyme
- Increased in metabolizing function or activity
<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>FUNCTIONAL DEFINITION</th>
<th>GENETIC DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizers</td>
<td>Increased enzyme activity</td>
<td>Two increased function alleles or more than 2 normal function alleles</td>
</tr>
<tr>
<td>Extensive metabolizers</td>
<td>Fully functional enzyme activity</td>
<td>Combinations of normal function and decreased function alleles</td>
</tr>
<tr>
<td>Intermediate metabolizers</td>
<td>Decreased enzyme activity</td>
<td>Combination of normal function, decreased function, and/or no function alleles</td>
</tr>
<tr>
<td>Poor metabolizers</td>
<td>Little to no enzyme activity</td>
<td>Combination of no function and/or decreased function alleles</td>
</tr>
</tbody>
</table>
Extensive Metabolizers (aka. “Normal”)

http://www.icp.org.nz/icp_t8.html
Intermediate Metabolizers

[Diagram showing genetic status: extensive metabolism (EM), intermediate metabolism (IM), poor metabolism (PM), ultrarapid metabolism (UM)]

http://www.icp.org.nz/icp_t8.html
Poor Metabolizers

http://www.icp.org.nz/icp_t8.html
Ultrarapid Metabolizers
Example: CYP2C9

► Alleles
  • Normal activity
    – CYP2C9*1
  • Decreased activity
    – CYP2C9*2, CYP2C9*3

► Phenotypes (3 groups)
  • Poor metabolizers (PM)
  • Intermediate metabolizers (IM)
  • Extensive metabolizers (EM)
  • *No ultrarapid metabolizer group for this enzyme*
**Example: CYP2C9**

<table>
<thead>
<tr>
<th>CYP2C9 PHENOTYPE</th>
<th>TEXT DESCRIPTION OF GENOTYPE</th>
<th>EXAMPLES OF GENOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive metabolizers (EM)</td>
<td>Two normal activity alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizers (IM)</td>
<td>One normal activity allele and one decreased function allele</td>
<td>*1/*2, *1/*3</td>
</tr>
<tr>
<td>Poor metabolizers (PM)</td>
<td>Two decreased function alleles</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
</tbody>
</table>

Frequency of CYP2C9*2: Caucasians (11%), Africans (1%), Asians (rare)
Frequency of CYP2C9*3: Caucasians (7%), Africans (1%), Asians (3%)
Example: CYP2C9

- CYP2C9*2 and CYP2C9*3 alleles are associated with decreased phenytoin dose requirements
  - WHY?

- CYP2C9*2 and CYP2C9*3 alleles are associated with increased INR in patients on warfarin
  - WHY?
Example: CYP2C9 and Phenytoin

- **HLA-B*15:02 genotype**
  - **HLA-B*15:02 carrier**
    - If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin.
  - **HLA-B*15:02 non-carrier**
    - **CYP2C9 genotype**
      - **CYP2C9 EM**
        - Initiate therapy with recommended maintenance dose.
      - **CYP2C9 IM**
        - Consider 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.
      - **CYP2C9 PM**
        - Consider 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.
Clinical Pharmacogenomics

- Drug Metabolizing Enzymes
- Drug Transporters
- Drug Targets

Pharmacokinetics
Pharmacodynamics

Variability in Efficacy or Toxicity

Drug Transporters

- Proteins encoded by genes
- Movement across membranes
- Superfamilies
  - ABC transporters (e.g., PGP)
  - SLC transporters (e.g., OATP1B1)
- Polymorphisms can lead to increased or decreased transport
Example: OATP1B1

► SLCO1B1 c.521 T>C SNP

► Alleles
  • Normal transporter function
    – SLC1B1*1A, SLC1B1*1B
  • Decreased transporter function
    – SLC1B1*5, SLC1B1*15, SLC1B1*17

► Phenotypes (3 groups):
  • Low function
  • Intermediate function
  • Normal function
Example: OATP1B1

<table>
<thead>
<tr>
<th>SLCO1B1 PHENOTYPE</th>
<th>TEXT DESCRIPTION OF DIPLOTYPE</th>
<th>EXAMPLES OF DIPLOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Two normal function alleles</td>
<td>*1A/*1A, *1A/*1B, *1B/*1B</td>
</tr>
<tr>
<td>Intermediate function</td>
<td>One normal function allele and one decreased function allele</td>
<td>*1A/*5, *1A/*15, *1B/*5</td>
</tr>
<tr>
<td>Low function</td>
<td>Two decreased function alleles</td>
<td>*5/*5, *5/*15, *17/*17</td>
</tr>
</tbody>
</table>
Statins require uptake into hepatocyte via OATP1B1 drug transporter. Once in hepatocyte, statins exert their therapeutic effects by inhibiting HMG-CoA reductase enzyme.

SLCO1B1 polymorphism is associated with _______ uptake into liver and __________ statin concentration.

Concentration-dependent toxicities are expected to _____? Efficacy will ______?
Clinical Pharmacogenomics

Drug Metabolizing Enzymes

Drug Transporters

Drug Targets

Pharmacokinetics

Pharmacodynamics

Variability in Efficacy or Toxicity
Pharmacodynamics

- What a drug does to the body and how it does it
- Drug receptor theory
- Non-receptor mediated reactions
Drug and Drug Receptor Interactions

1) Gated ion channels
2,3) Transmembranous receptors
4) G protein-coupled receptors
5) Intracellular receptors

Drug Targets

- Genetic polymorphisms encoding drug target proteins may lead to variability in drug response (PD)

- **Effects**
  - May increase or decrease protein synthesis of drug targets
  - May alter receptor or enzyme configuration, disabling its ability to function

- *More complicated than pharmacokinetics due to complexity of drug-receptor response*

- **Examples**
  - HLA loci and drug-induced hypersensitivity
  - VKORC1 and warfarin response
Pharmacogenomics in Clinical Practice

- Pharmacogenomics Knowledge Base (PharmGKB)
  - Knowledge source that collects, curates, and disseminates impact of human genetic variation on drug response

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - Peer-reviewed, evidenced-based clinical guidelines for select drug-gene pairs
  - Designed to help clinicians understand how available genetic test results should be used to optimize drug therapy

- Others also
Pharmacogenomics in Pediatrics

- Most PGx studies with adult populations
  - Issues?

- Some Children’s Centers using PGx in clinical care

- Examples
  - Cancer
  - Immunosuppression
  - Cancer
# Pharmacogenomics Resources

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>WEBSITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PharmGKB</td>
<td><a href="http://www.pharmGKB.org">www.pharmGKB.org</a></td>
</tr>
<tr>
<td>CPIC</td>
<td><a href="https://cpicpgx.org/">https://cpicpgx.org/</a></td>
</tr>
<tr>
<td>All of Us (Precision Medicine Initiative)</td>
<td><a href="https://allofus.nih.gov/">https://allofus.nih.gov/</a></td>
</tr>
<tr>
<td>Genetics and Genomics Competency Center</td>
<td><a href="http://www.genomicseducation.net/">http://www.genomicseducation.net/</a></td>
</tr>
<tr>
<td>National Human Genome Research Institute (NIH)</td>
<td><a href="https://www.genome.gov/">https://www.genome.gov/</a></td>
</tr>
<tr>
<td>Genetics Genomics Competency Center (G2C2)</td>
<td><a href="https://genomicseducation.net/">https://genomicseducation.net/</a></td>
</tr>
</tbody>
</table>
Pharmacogenomics Resources

https://genomicseducation.net/competency
Nurse Competencies

1 PR: PROFESSIONAL RESPONSIBILITIES
- PR-1: Recognize one's own attitudes and values
- PR-2: Advocate for clients' access
- PR-3: Examine competency of practice
- PR-4: Incorporate genetic and genomic technologies and information into practice.
- PR-5: Demonstrate the importance of tailoring genetic and genomic information and services
- PR-6: Advocate for the rights of all clients

2 NA: NURSING ASSESSMENT

3 ID: IDENTIFICATION

4 RA: REFERRAL ACTIVITIES

5 PECS: PROVISION OF EDUCATION, CARE AND SUPPORT

https://genomicseducation.net/competency/nurse
Thank you