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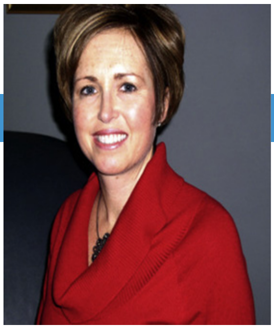

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Pharmacogenomics in Pediatrics: Personalized Medicine Showing Eminent Promise

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ALTHOUGH CLINICIANS ATTEMPT to individualize medication dosages for patients based on weight, age, allergies, organ function, and past drug reactions, responses can vary widely. It is likely that a patient's genetic make-up may account for a considerable disparity in response to treatment or even an adverse drug reaction (ADR) (Beery & Workman, 2012). This disparity has affected healthcare costs and quality, with efficiency rates of commonly prescribed drugs estimated to be between 25%–80% (Visscher et al., 2011). In addition, ADRs in the U.S. are estimated to cost $100 billion annually, form the basis of severe morbidity and mortality issues, and account for 7% of hospital admissions (Visscher et al., 2011).

Pharmacogenomics has the potential to significantly improve patient outcomes. Pharmacogenomics is the science of analyzing a patient's deoxyribonucleic acid (DNA), recognizing gene variations in response to certain drugs, and thereby making drugs safer and more efficient (Prows, 2011). Pharmacogenomics is quickly becoming a field of research that will change how drugs are prescribed and delivered in the future. As pharmacogenomics research continues to evolve and becomes the mainstay of treatment, nurses need to understand the association among genetics, treatment choice, and patient response (Bartlett, 2011).

Establishing the phenotype and genotype relationship through genetic testing is starting to filter its way down to pediatric patients and is beginning to impact decisions for clinical application. The Food and Drug Administration (FDA) now strongly recommends that genetic testing be performed in children before initiating treatment specifically for cancer, human immunodeficiency virus (HIV), and anticoagulant therapy (Kitzmiller, Groen, Phelps, & Sadee, 2011). This article provides a review of pharmacokinetics, an explanation of enzyme and gene metabolism, available pharmacologic testing, and case studies that illustrate implications for pediatric patients.

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Overview of Genetic Basics and Pharmacokinetics

The human genome consists of 23 base pairs of chromosomes that are composed of chunks of DNA. The DNA molecule is a double helix consisting of two bound strands of polynucleotide that resemble a spiral staircase. The building blocks of the spiral staircase are the four-nucleotide bases, which consist of adenine, guanine, thymine, and cytosine. Each polynucleotide strand is a sequential string of the four-nucleotide bases and forms a base pair (Howland, 2012). The arrangement of these DNA base pairs along the chromosome is called the DNA sequence or codon. The DNA genes establish the structure as well as the function of proteins (Howland, 2012). Differences in individual genetic makeup alter the structure or the function of proteins that participate in the key operation of pharmacokinetics (how the body processes a drug) and pharmacodynamics (how drugs affect the body) (Kitzmiller et al., 2011). Pharmacokinetic processes are manipulated by the proteins created by numerous distinctive genes and are often inherited in either autosomal dominant or recessive patterns (Prows, 2011). Of

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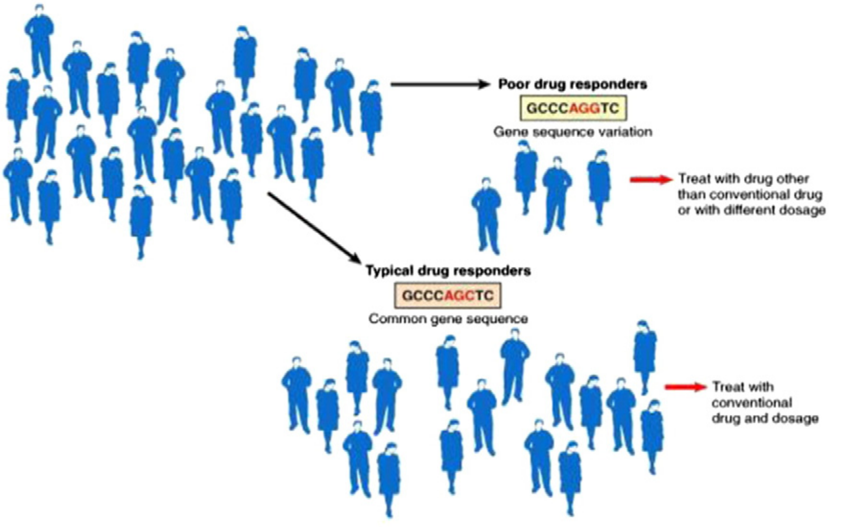
course, various other measures such as age, body mass index, and comorbid conditions can affect drug responses, dosages, and therapeutic effects.

Everybody inherits two copies of each gene; these genes are similar but not identical. DNA sequences of the same genes in the general population are very similar and normally occur in a specific sequence; a common gene in the general population is often referred to the “wild type gene” (Court, 2007 & Prows, 2011). When the normal sequence of genetic bases is substituted (a switch of a letter or nucleotide), the gene function is changed and called genetic polymorphism or a single nucleotide polymorphism (SNP) (Bartlett, 2011) (Figure 1). Because human beings have 2 copies of a particular gene inherited from their mother or father, the SNP can exist in either one single copy of the gene (homozygous) or in both copies of the gene (heterozygous). The net effect of the SNP on the gene function may depend upon if one or two copies of the gene are altered (Howland, 2012). The function of a gene may be distorted depending upon where the SNP is located in relation to the gene (Court, 2007; Howland, 2012). Collections of SNPs or other different genes are located close to each other on a chromosome; when inherited together, this is called a HapMap or haplotype (Howland, 2012). Discovery of genetic polymorphisms or SNPs could identify nonfunctional, superfunctional, or absent proteins, which modify a gene’s drug coding metabolism enzymes, drug transporters, and receptors (Beery & Workman, 2012). This is the basis for pharmacogenetic research and the commercial expansion of pharamcogenetic testing (Howland, 2012).

Metabolizing Enzymes and Genes

The Cytochrome P450 enzyme system (CYP450) is found in the liver and is accountable for metabolism of numerous drugs (Prows, 2011). CYP450 enzymes have become a priority of investigation for researchers. Each one of these enzymes are associated with a gene and are labeled CYP, followed by an Arabic number, a letter, and then another Arabic number (Prows, 2011). Thus, CYP2D6 gene encodes for the CYP2D6 enzyme. The CYP2D6 enzyme by itself is accountable for metabolism of 30% of prescribed drugs, which consist of many beta-blockers, antiarrhythmics, antidepressants, antipsychotics, and opioids (Beery & Workman, 2012). An individual’s ethnic or ancestral background also influences how CYP genes perform during drug metabolism; for example CYP3A5 is not expressed in most Caucasians; however, it is expressed in about 50% of African Americans (Bell, 2012). In addition, drug metabolism is affected by ontogeny (development of an individual). An illustration of ontogeny is the low levels of CYP 3A4 expression in newborn infants causing their inability to clear the drug Cisapride. Subsequently, Cisapride was removed from the U.S. market due to ADRs that it caused, including deadly cardiac arrhythmias in some patients (Hines & Mc Carver, 2006). Hence, the clinical reaction to the variation in the genetic code can create a wide range of patient responses to a drug, from severe toxic side effects to a non-drug responder (Figure 1.). Often in clinical practice, the phenotype (visible drug reaction or disease) is recognized before the genotype (coding sequence of DNA base pairs) is identified (Prows, 2011).



Pharmacogenetics is the study of genetic differences in the alleles associated with individual variability in drug response. Patients with the same diagnosis respond differently because of allelic difference: in this example, the normal gene sequence is GCCCAGCTC but the mutation gene sequence is GCCCAGGTC. The AGC in the sequence of the normal gene codes for serine, but the AGG in the mutation gene’s sequence codes for arginine. The substitution of arginine for serine in the drug-metabolizing enzyme molecule will cause the enzyme to be less effective or ineffective; this person is considered a “poor drug responder.” The practice of pharmacogenetics involves genotyping patients and treating those who would be “poor drug responders” with a drug other than the conventional drug or with a different dosage.

Figure 1 The Effects of Gene Polymorphisms on Drug Action and Metabolism. McLeod, H. (2010). Lecture 10. NHGRI Current topics in genome analysis: Pharmacogenomics. Retrieved from http://www.genome.gov/Pages/Research/IntramuralResearch/DIRCalendar/CurrentTopicsinGenomeAnalysis2010/CTGA2010_Lec10_.