The basics of pharmacogenomics: Review the basics of genomics and available tests

Megan Ehret, PharmD, BCPP[1]

[1]Assistant Professor, University of Connecticut, Hartford, CT

ABSTRACT

Pharmacogenomics, which is the study of genes that determine drug behavior, is a field which has seen an increase in research and discoveries which impact the diagnosis and treatment of various disease states. This article reviews the basic concepts of pharmacogenomics and the genomic tests which are currently available.

KEYWORDS

pharmacogenomics, pharmacogenetics, genome

The way in which a person responds to a drug, whether it be good or bad, is dependent on many variables including genetic make-up. The term Pharmacogenetics, coined in 1959 by Vogel (Vogel F. [Modern problems of human genetics.] Ergeb Inn Med Kinderheilkd. 1959;12:52-125. In German), is the study of inherited variations in drug metabolism and response. The term is commonly used interchangeably with Pharmacogenomics, which is the general study of all genes that determine drug behavior (http://www.ncbi.nlm.nih.gov/About/primer/pharm.html).

The Human Genome Project, undertaken in 1990 to identify the approximately 20,000 to 25,000 genes in human DNA and to determine the sequences of its 3 billion base pairs, has helped accelerate pharmacogenomics. The knowledge of the human genome will continue to be analyzed for years to come to determine the effects of DNA variations among individuals which could lead to new ways to diagnose, treat, and potentially prevent thousands of disorders (http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml).

The International HapMap Project is a multi-country effort to publicly identify and catalog genetic similarities and differences in humans. The countries involved in the project include: Canada, China, Japan, Nigeria, United Kingdom, and the United States. The goal of the project is to compare the genetic sequences of different individuals to identify chromosomal regions where genetic variants are shared (http://hapmap.ncbi.nlm.nih.go/hapmappopulations.html.en).

With completion of both the Human Genome Project and the International HapMap Project, along with the increase in genetic technologies, there has been an increase in research and discoveries in pharmacogenomics impacting diagnosis and treatment of many disease states.

CONCEPTS IN PHARMACOGENOMICS:

The human genome consists of approximately three billion base pairs, and their sequence varies among individuals. These variations can include the following:

1. Base insertions or deletions: Extra base pair(s) are added (insertions) or removed (deletions) from the DNA of a gene. Cells read DNA in 3 letter (base) "words", so adding or removing one letter can have devastating consequences and can make the DNA meaningless (Frameshift mutation). It often results in a shortened protein.
2. Single nucleotide polymorphisms (SNPs): a DNA sequence variation that occurs when a single nucleotide in the genome is altered. The variation must occur in $\geq$1% of the population to be recognized as a SNP. They occur every 100 to 300 base pairs.
3. Copy-number variations: The number of copies of a particular gene varies from one individual to another. The extent to which copy-number variations contribute to human disease is not known. Several cancers have been associated with elevated numbers of particular genes.
4. Variable number tandem repeats: A linear arrangement of multiple copies of short repeated DNA sequences that vary in length and are highly polymorphic. They are useful in linkage analysis.

Any of these variations can change the function of proteins that interact with a drug, which then alter individual responses to this drug. These alterations could be positive, negative, or neutral. A positive response would be an increase in efficacy from a particular drug. Negative responses include an increase in adverse effects

or a lack of efficacy from a particular medication. Neutral responses indicate either no change in the protein encoded by the gene, or the change has no effect on the protein function or gene expression.

Pharmacogenomics of Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (absorption, metabolism, distribution, or excretion of a drug) can be affected by a patient's genetic make-up. Altering the concentration of the parent drug or its active metabolites at the site of drug action may alter the response to the medication. A primary example would be the Cytochrome P450 System (CYP) system. Patients can have varying metabolic rates of drugs broken down through the CYP system, with individuals classified as ultra-rapid, intermediate, extensive, or poor metabolizer status (http://www.cypalleles.ki.se/) (Table 1).

Table 1: Metabolizer Status Classifications

Ultra-rapid	Extreme metabolic activity, which may result in poor efficacy and therapeutic failure of the drug
Extensive	Normal to high metabolic activity
Intermediate	Impaired or slow metabolic activity
Poor	Low to absent metabolic activity, which may result in a higher risk of toxicity

Currently, there are FDA approved mechanisms for determining genotype and predicted metabolizer status (phenotype) for CYPs 2C9, 2C19, and 2D6.

Pharmacodynamics, the action or effects of drugs on the body, can also be altered by the genetic make-up of a patient. These genetic polymorphisms can change the activity of the drug target, which may alter the drug response. Examples would include the serotonin transporter gene polymorphisms and the dopamine receptor gene polymorphisms.

Available Genomic Tests

Currently there are two ways in which a genetic test can be introduced in practice. The first mechanism is for the FDA to grant approval as an in vitro diagnostic device. There are currently six approved devices (Table 2). The second method bypasses the FDA. There are currently >1300 tests available which are not FDA approved, but are currently being performed at labs which are subject to quality testing. The testing is regulated by the Clinical Laboratory Improvement Amendment of 1988 (http://www.nhpf.org/pdfs_bp/BP_Pharmacogenomics_01-28-08). (http://www.geneticalliance.org/ws_display.asp?filter=policy.genetic.testing)

Table 2: Approved Genomic Tests

Test (Manufacturer)	Drug	Gene
Verigene warfarin metabolism nucleic acid test (Nanosphere, Northbrook, IL)	Warfarin	CYP2C9, VKORC1
Infiniti 2C9-VKORC1 multiplex assay (AutoGenomics, Carlsbad, CA)	Warfarin	CYP2C9, VKORC1
Paragon Dx rapid genotyping assay (Paragon Dx, LLC, Morrisville, NC)	Warfarin	CYP2C9, VKORC1
eSensor warfarin sensitivity (Osmetech Molecular Diagnostics, Pasadena, CA)	Warfarin	CYP2C9, VKORC1
Invader UGT1A1 molecular assay (Third Wave Technologies, Madison, WI)	Irinotecan	UGT1A1 (uridine diphosphate glucuronyltransferase)
AmpliChip CYP450 test (Roche Diagnostics, Indianapolis, IN)	Any medication metabolized through these systems- including antidepressants and antipsychotics	CYP2C19, CYP2D6

CANDIDATE GENE VERSUS GENOME-WIDE ASSOCIATION STUDIES

Candidate Gene Studies

This approach tests whether a particular allele or a set of alleles is more frequent in patients who have either a better or worse drug response. The genes are typically selected based on their known physiological or pharmacologic effect on disease or drug response. Prior knowledge of a gene's function is required to select it for analysis in this type of study. If there are too many known SNPs to study, the numbers may be reduced either by setting the minor allele frequency to >5% or by using the

degree of linkage disequilibrium, phenomenon whereby genetic variants are associated: people who have one tend to have a second one, among the SNPs. SNPs that are in strong linkage disequilibrium form haplotypes. Genotyping at one locus enables inference of genotypes at other loci in a haplotype. The SNP that is genotyped and used to infer the genotypes at the other loci in a haplotype is called a tag SNP. When genotyping only the tag SNPs, the total number of SNPs needed can be reduced without comprising the required coverage of the genetic variations in the gene. This type of testing is useful to study a genetic association with drug response. This also requires a smaller sample size than Genome Wide Association Studies. The downfall to candidate gene studies is the requirement of prior knowledge of the interaction of the gene and drug response. If this information is limited, the selection of the gene to study can be difficult to justify.

Genome Wide Association Study (GWAS)

The GWAS surveys the common genetic variations for a role in disease or drug response by genotyping large sets of SNPs (typically tag SNPs) across the genome. Most GWASs have been conducted as case-control, cohort, or family studies. The goal is to determine whether a particular allele or set of alleles is more common in patients with a certain disease or a better/worse drug response. GWAS does not hypothesize a possible role of a gene in the drug response; it is a useful tool to discover new functions of a gene or to identify a new genetic biomarker that could be used as a surrogate for drug response. The limiting factors in using GWAS are the requirement for a large clinical sample size and the high cost of whole-genome SNP panels.

REFERENCES

1. Chan IS, Ginsburg GS. Personalized medicine: progress and promise. Annu Rev Genomics Hum Genet. 2011;12:217-44. DOI: 10.1146/annurev-genom-082410-101446. PubMed PMID: 21721939.
2. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. Transl Res. 2009;154(6):277-87. DOI: 10.1016/j.trsl.2009.09.005. PubMed PMID: 19931193.
3. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. Cleve Clin J Med. 2011;78(4):243-57. DOI: 10.3949/ccjm.78a.10145. PubMed PMID: 21460130.
4. Shin J, Kayser SR, Langaee TY. Pharmacogenetics: from discovery to patient care. Am J Health Syst Pharm. 2009;66(7):625-37. DOI: 10.2146/ajhp080170. PubMed PMID: 19299369.
5. Somogy A. Evolution of pharmacogenomics. Proc West Pharmacol Soc. 2008;51:1-4. PubMed PMID: 19544663.
6. Squassina A, Manchia M, Manolopoulos VG, Artac M, Lappa-Manakou C, Karkabouna S, et al. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. Pharmacogenomics. 2010;11(8):1149-67. DOI: 10.2217/pgs.10.97. PubMed PMID: 20712531.

How to cite this editor-reviewed article
Ehret M. The basics of pharmacogenomics: Review the basics of genomics and available tests. Ment Health Clin [Internet]. 2012;1(9):207-9. Available from: http://dx.doi.org/10.9740/mhc.n99714