# Pharmacogenetics in Heart Failure: How It Will Shape the Future

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**KEYWORDS**

• Heart failure • Pharmacogenomics • Gene mutations
• Genetics • Single nucleotide polymorphisms

Pharmacogenomics is a growing field of research that focuses on how an individual's genetic background influences his or her response to therapy with a drug or device. Recent studies suggest that an individual's genetic background combined with environmental factors can predict the occurrence of disease, an individual's response to pharmacologic interventions, drug toxicity, or prognosis. Increasing evidence from clinical trials in patients with heart failure (HF) due to systolic dysfunction suggest that genetic variations can predict the occurrence of HF, influence the effects of standard therapies, and influence outcomes of HF patients. This article reviews the underlying principles of pharmacogenomics, discusses some of the complex variables that influence the investigational approach to pharmacogenomics, demonstrates how variations in genes encoding a variety of different proteins can influence the effects of pharmacologic agents, and describes the potential impact of pharmacogenomics on the treatment of patients with HF (**Table 1**).

## PHARMACOGENOMICS: A HISTORICAL PERSPECTIVE

That different individuals respond differently to the same ''drug'' or substance has been known since the earliest days of the practice of medicine. For example, in 510BC Pythagoras noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all, individuals.[1] In the 1950s, alterations in glutathione metabolism were detected in the erythrocytes of patients with hemolytic anemia that were induced by ingestion of a variety of agents including fava beans, and ''Favism'' was attributed to glucose-6-phosphate dehydrogenase (G6PD) deficiency.[2,3] Another major observation of genetic variation in drug response dating from the 1950s involved the muscle relaxant suxamethonium chloride, a drug metabolized by *N*-acetyltranseferase.[4] One in 3500 Caucasians was found to have a less efficient variant of the enzyme (butyrylcholinesterase) that metabolizes suxamethonium chloride. In patients with the variant, the drug's effect is prolonged because of slow metabolism, resulting in delayed recovery from surgical paralysis. Patients with ''normal'' *N*-acetyltransferase activity were referred to as ''fast acetylators'' while those with the decreased enzyme activity were referred to as ''slow acetylators.'' Because many drugs undergo acetylation, this variant also influenced how people responded to a family of drugs including isoniazid (antituberculosis) and procainamide (antiarrhythmic).[5]

Attempts to understand such variations led to family, twin, and racial distribution studies that focused on plasma concentrations and the factors known at the time to influence drug levels, including absorption, distribution, metabolism, and excretion.[6] These studies demonstrated that the G6PD enzymatic defect in erythrocyte metabolism was inherited and that there was a higher

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Heart Failure Clin 6 (2010) 1–10
doi:10.1016/j.hfc.2009.08.013
1551-7136/09/$ – see front matter 

**Table 1**
**Terminology**

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| Genotype | A person's genetic makeup, as reflected by his or her DNA sequence |
| Phenotype | The clinical presentation or expression of a specific gene or genes, environmental factors, or both |
| Heterozygous | Having 2 different alleles at a specific gene locus |
| Homozygous | Having 2 identical alleles at a specific gene locus |
| Allele | Different variations of the same gene |
| Haplotype | A combination of alleles or sequence variations on the same chromosome |
| Codon | A 3-base sequence of DNA or RNA that specifies a single amino acid |
| Exon | A region of a gene that codes for a protein |
| Intron | A region of a gene that does not code for a protein |
| Penetrance | The likelihood that a person carrying a particular mutant gene will have an altered phenotype |
| Genetic polymorphism | Monogenic variations that exist in the normal population in a frequency of more than 1% |
| Single-nucleotide polymorphism (SNP) | A common variant in the genome sequence; the human genome contains about 10 million SNPs |
| Nonsynonymous | A mutation that produces a protein that takes on a new or enhanced function |
| Synonymous | A mutation that produces the same protein |
| Alternative splicing | A regulatory mechanism by which variations in the incorporation of a gene's exons, or coding regions, into messenger RNA lead to the production of more than one related protein, or isoform |
| Nonsense mutation | Substitution of a single DNA base that results in a stop codon, thus leading to the truncation of a protein |
| Regulatory mutation | A mutation in a region of the genome that does not encode a protein but affects the expression of a gene- promoter region |
| Point mutation | The substitution of a single DNA base in the normal DNA sequence |