Chapter 10
Pharmacogenomics and Cardiovascular Disease

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ABSTRACT

Cardiovascular disease is one of the most prevalent disease states in the U.S. and contributes substantially to overall morbidity and mortality. The ability to effectively optimize the treatment of cardiovascular disease has a significant impact on overall disease prevention and treatment. This chapter discusses the relationship between genetic variations and their impact on medications used for the treatment of cardiovascular disorders. Key medications that are susceptible to genetic variation have been identified. The chapter describes the mechanisms by which genetic variation may contribute to altered medication concentrations or effects and briefly reviews the place in therapy for the cardiovascular medications. In addition, this chapter reviews current clinical literature to determine the overall impact these variations may have on clinical outcomes.

INTRODUCTION

The prevalence of cardiovascular disease in the United States is extensive. The American Heart Association estimates that approximately 1 in 3 American adults have at least one cardiovascular condition. Many have multiple conditions. Eighty million Americans are estimated to have hypertension, while 15 million have some form of coronary heart disease. Cardiovascular disease (CVD) encompasses a wide-variety of conditions including hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation and other arrhythmias, and congestive heart failure. CVD accounts for about 30% of all deaths in the United States and is the leading cause of death for both men and women (Mozafarian et al., 2016).

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Evidence-based therapies of various pharmacologic agents have been shown to reduce morbidity and mortality. Commonly used agents may include beta-blockers, statins, anti-platelets, and anti-coagulants (January et al., 2014; O'Gara et al., 2013; Yancy et al., 2013). The effects of these medications may be profoundly altered by genetic variation among patients in genes responsible for drug metabolism, drug transport or the targets of the drugs themselves. The clinical implications of these genetic variations will be discussed in this chapter.

BACKGROUND

It has been a little over a 15 years since the publication of the initial draft of the human genome (Venter et al. 2001; Lander et al. 2001). Estimates for the final cost to sequence the "first" human genome range from $500 million to $1 billion. Since the completion of this first genome sequencing, technologies have undergone two revolutions first with massively parallel sequencing in the 2005 and recently with nanopore sensing technologies that hold out the hope of single molecule sequencing. As these next generation sequencing technologies become readily available, genome sequencing costs has decreased and sequence yields increased exponentially. In large part due to availability of high-throughput sequencing technologies it has become possible to begin to assess and catalogue human genetic variation. In an analysis of sequence data from protein coding regions (exomes) of 60,706 individuals Lek, et al. (2016) have identified over 3,000 genes which are likely loss of function variants; importantly 72% of these identified genes have no established disease phenotype at this time. The ultimate identification and delineating of these variants in human populations are critical to understanding the underlying genetic causes of human disease and drug response.

This revolution in genomic technologies as well as the attendant advances in bioinformatics has led to the appeal for prevention and treatment strategies based upon the individual characteristics of the patient, now referred to as "Precision Medicine".

The recognition that much of the variability among patients in disease severity and treatment response may soon be anticipated (and prevented) with knowledge being acquired in the new fields of genomics, metagenomics (assessment of the patient's microbial community), metabolomics (assessment of the small molecule metabolites in biological systems) and proteomics (assessment of the patient's proteins including enzymes, transporters, receptors) drives the development of precision medicine. Importantly, one of the more successful areas in precision medicine is in pharmacogenetics or pharmacogenomics. The two terms have been used interchangeably and have the ultimate goal of identifying the many underlying genetic factors playing a role in the efficacy or toxicity of all drugs. Pharmacogenetics traditionally considers the action of a single gene in drug response. Pharmacogenomics is the broader term and includes any and all genes and their interactions that may play a role in drug response. Pharmacogenetics/genomics has experienced more success in terms of clinical relevance as compared to success of genomics to predict disease risk because often a single gene will play a large role in drug response and is thus a much more tractable problem (Altman 2011).

For virtually all medications the role of patient variability in drug response either in efficacy, toxicity or adverse reactions is well known. One aspect of patient variability is the incidence of adverse drug reactions (ADR). For example, the Institute of Medicine has estimated that there are ~1.5 million pre-

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