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Genetic Polymorphisms in Coronary Heart Disease

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Table of Contents

Introduction	2
Human DNA Polymorphisms	2
Clinical Genetics	3
Molecular Genetics	3
Candidate Genes	6
Summary	10
References	10

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I. INTRODUCTION

Coronary heart disease (CHD) is a complex phenotype caused by the interaction of multiple genetic and environmental factors. Because CHD is a major cause of morbidity and mortality, much effort has been focused on identifying risk factors and devising strategies to mitigate their effects (Table 1).¹ These risk factors include biochemical and physiologic variables associated with increased risk of atherosclerosis, such as lipid levels, blood pressure, and insulin resistance.² Advances in molecular genetics have identified many potential genetic risk factors for CHD and myocardial infarction (MI), such as variants of genes involved in lipid metabolism, vascular homeostasis, and thrombosis.³ Recent reports suggest that at least 100 loci affect susceptibility to CHD and MI.

Functional variants of angiotensin-1-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), cholesteryl ester transfer protein (CETP), β -fibrinogen, plasminogen activator inhibitor-1 (PAI-1), glycoprotein (GP) IIIa, methylenetetrahydrofolate reductase (MTHFR), and many apolipoprotein genes may be pos-

sible risk factors for CHD and MI. Understanding the complex interaction between these factors is expected to provide substantial insights into the pathogenesis of CHD and MI and to lead to the development of genetic-based risk stratification, prevention, and treatment.

II. HUMAN DNA POLYMORPHISMS

A valuable tool underlying the recent progress in molecular diagnosis is the ability to visualize sequence differences in DNA (Figure 1). In the context of a population, these differences are called polymorphisms.⁴ Genetic polymorphisms underlie the diversity of humans. Each of us carries a vast library of different polymorphisms. Genetic variation is common from person to person and is usually of no phenotypic consequence. Benign changes may occur in regions that do not encode protein, or changes may not alter the properties of the protein encoded by the gene. The challenge in the molecular diagnosis of gene mutations is twofold: to find the rare alteration in sequence and to distinguish important changes from benign polymorphisms.