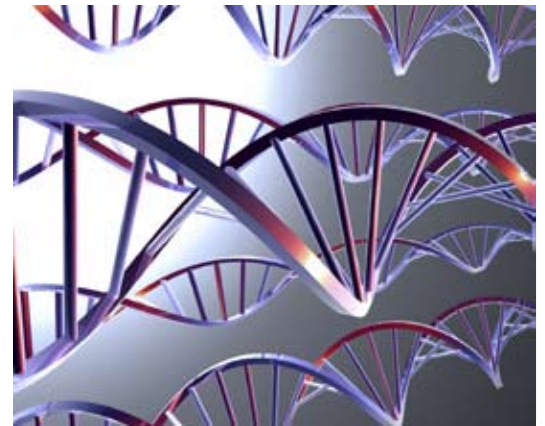


## The Genomics of Cardiovascular Disease

Although the June 2000 New York Times headline, “Genetic Code of Human Life is Cracked by Scientists,” appeared to herald the arrival of the ‘genetic age,’ according to Eric J. Topol, MD, Scripps Translational Science Institute, La Jolla, CA, it has been the numerous and stunning breakthroughs in single nucleotide polymorphisms (SNP) in the last year that has ushered in the “age of the genome.” A SNP is a DNA sequence variation that occurs when a single nucleotide differs between members of a species in at least 1% of the population. SNPs are useful for comparing regions of the genome between cohorts with and without a particular disease.



The identification of SNPs has created a ‘genomic gold rush’ to discover associations between a disease process and SNP variants. Over 40 diseases have undergone genome-wide association studies (GWAS) to identify common genetic factors that influence health and disease. In a GWAS that was undertaken in the British population that examined approximately 2000 individuals for each of seven major diseases and a shared set of approximately 3000 controls, 24 independent association signals at  $P < 5 \times 10^{-7}$  were identified, including one in bipolar disorder, one in coronary artery disease, nine in Crohn’s disease, three in rheumatoid arthritis, seven in type 1 diabetes, and three in type 2 diabetes [Wellcome Trust Case Control Consortium. *Nature* 2007].

Whole genome information, when combined with clinical and other phenotype data, offers the potential for increased understanding of basic biological processes that affect human health, improve risk prediction, disease prevention, and patient care. Ultimately, the realization of the promise of personalized medicine, which Dr. Topol believes will be readily available by the year 2015, would permit clinicians to deliver optimal therapies to their patients.

There are six diseases that have an extensive genomic definition: type 2 diabetes, Crohn’s disease, breast cancer, age-related macular degeneration, prostate cancer, and systemic lupus erythematosus. Of particular interest to cardiologists, SNPs have been defined for myocardial infarction (MI), coronary artery disease (CAD), atrial fibrillation (AF), lipoprotein disorders, and hypercholesterolemia.

Two common sequence variants on chromosome 9p21, tagged by rs10757278-G and rs10811661-T, affect the risk of MI [Helgadottir A et al. *Science* 2007]. Approximately 21% of individuals in the population are homozygous for these variants, and their estimated risk of suffering an MI is 1.64 times as great as that of non-carriers. The same sequence variant on 9p21 that is associated with MI is also associated with abdominal aortic aneurysms and intracranial aneurysms [Helgadottir A et al. *Nat Genet* 2008]. However, to date there are no studies that show how these markers develop into the disease state.

Another recent GWAS has identified variants on chromosome 9p21.3 that affect the risk of CAD. The risk allele (C) of the lead SNP, rs1333049, was significantly associated with

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CAD ( $p < 0.05$ ). In a pooled analysis, the odds ratio per copy of the risk allele was 1.29 (95% CI, 1.22 to 1.37;  $p = 0.0001$ ). An autosomal-additive mode of inheritance best explained the underlying association [Schunkert H et al. *Circulation* 2008].

Two sequence variants on chromosome 4q25 that are adjacent to PITX2 (which has a critical function in left-right asymmetry of the heart) confer risk of AF. The association is inversely related to age. About 35% of individuals of European descent have at least one of the variants, and the risk of AF increases by 1.72 and 1.39 per copy [Gudbjartsson DF et al. *Nature* 2007]. Nine validated SNP variants on chromosome 1p13.3 have been associated with modulation in levels of LDL or HDL cholesterol, and the incorporation of them into a genotype score improved clinical risk reclassification in a cardiovascular cohort when added to standard clinical factors [Kathiresan S et al. *N Engl J Med* 2008; Sandhu MS et al. *Lancet* 2008].

Dr. Topol believes that this ‘treasure trove’ of genetically linked lipoprotein biology may lead to novel therapeutic interventions if a few caveats can be overcome. He cautioned that we are still working with incomplete coverage of the genome and that structural variants are complex and much larger than initially hypothesized [Korbel JO et al. *Science* 2007]. Structural variation of the genome involves kilobase- to megabase-sized deletions, duplications, insertions, inversions, and complex combinations of rearrangements. Epigenomics (processes that regulate how and when genes change) and epistasis (when the action of one gene is modified by one or more genes) are not completely understood and may impact the disease process in unpredictable ways. In many cases, the observed effects actually result from multiple SNPs that act in concert within a gene, and thus analysis of a few variants per gene is not likely to be sufficient to identify potential functional effects.

Nonetheless, the ‘age of the genome’ is truly upon us, with private companies beginning to offer genome “scans” that claim to have the ability to predict the risk of many types of diseases. Next to come will be a consumer genome movement and genetic home testing kits. The physician needs to be prepared for the day when patients begin showing up in their offices with individual SNP profiles asking for interpretation of their health risk factors. Dr. Topol’s final comment was presented in a slide titled “The Resequencing Imperative”—“..when genome-wide resequencing is practical and affordable, it will be increasingly difficult for the genomic basis of health and disease to be left undetected.”

## Cardiac Infections

The first symposium developed jointly by the American College of Cardiology and the Brazilian Society of Cardiology, provided an overview of infectious diseases of the heart. The session featured an important review of viral and parasitic infections of the heart and the role of infection in myocarditis, pericarditis, and coronary artery disease CAD.

In her presentation, Dr. Maria de Lourdes Higuchi, MD, PhD, The Heart Institute, Sao Paulo, Brazil focused on *Chlamydia pneumoniae* (CP) and *Mycoplasma pneumoniae* (MP), 2 microorganisms that have been implicated in bacterial infection and inflammatory conditions of the heart and pericardium. MP requires cholesterol for survival, and because vulnerable atheromas are rich in cholesterol, they may provide a favorable environment for MP growth. Studies have confirmed that MP is found primarily in the lipid core of ruptured thrombosed plaques. In addition, mycoplasma may increase the virulence of other infectious agents; for example, Dr. Higuchi noted that research has demonstrated a symbiotic relationship between *Mycoplasma hominis* and *Trichomonas vaginalis* [Dessi et al. *Infect Immun* 2005]. “Species interaction forms more stable and productive colonies,” she said. The result is more resistant chronic infections.

In CAD, coinfection with MP and CP may represent an important contributor to plaque inflammation, instability, and rupture, because greater amounts of MP and CP have been strongly correlated with histologic signs of increased plaque vulnerability. In other studies, CAD or myocardial infarction (MI) has been found to be more prevalent among individuals who are seropositive for both MP and CP, and elevated levels of serum MP and CP antibodies have been found in association with acute MI.

Dr. Higuchi also noted that small amounts of MP and CP have been found in some vessels without atherosclerotic plaque, suggesting that another factor may contribute to the proliferation of these microorganisms. Her research has shown that vulnerable plaques also contain archaea, the most primitive microorganisms [Clinics 2006]. The powerful antioxidative enzymes of archaea may enable them to enhance the survival of aerobic microorganisms such as MP and CP and to participate in the pathogenesis of plaque vulnerability, said Dr. Higuchi. She added that effective treatment will require targeting the fundamental pathways that maintain the symbiotic state of the microorganisms.