Editorial

Molecular genetics of myocardial infarction: many genes, more questions than answers

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This editorial refers to “Genotypes and haplotypes predisposing to myocardial infarction: a multilocus case-control study” by Martin D. Tobin et al. on page 459.

In his 1999 Schattuck lecture to the Massachusetts Medical Society, Francis Collins provided an exciting vision of the development of genetically based, individualised preventive medicine by 2010. According to that vision, within a decade or two it should be possible to sequence anyone’s entire genome for a laboratory cost of less than $1000. This would allow clinicians to provide personalised advice on environmental risk and to adapt prevention and treatment to an individual’s genotype. Four years after that lecture, however, the vision of genomic medicine is not likely to materialise anytime soon.

Coronary artery disease (CAD) and myocardial infarction (MI) are complex diseases that result from a life-long interplay between genetic and environmental factors. To assess an individual’s risk, clinicians currently use score matrices based on traditional clinical and biochemical risk factors, such as the US Framingham score and the European SCORE. Genotypic information of interest includes common gene variants or polymorphisms (= gene variants with a prevalence ≥1% of the rare allele in the population) ranging from single nucleotide substitutions (single nucleotide polymorphisms or SNPs) to insertions or deletions in the DNA sequence, a variable number of repeats of two or more nucleotides (VNTRs), and haplotypes. The latter incorporate the pattern of allelic variation obtained by looking at more than one locus of genetic variation in the DNA sequence of a gene (or the entire chromosome) of a given individual.

Although many candidate genes that code for proteins known or suspected to be involved in the pathophysiology of atherosclerosis have been studied, early reports of positive associations between genotype and phenotype (generally observed in small studies) were mostly not replicated in larger cohorts. Although there can be valid reasons for non-replication, including multiple causative genes and disease mechanisms, gene–environment interactions, and population heterogeneity, conflicting reports are common and perplexing, casting doubts on this type of studies. Moreover, only genetic variants that impart a relative risk of two or more (which is comparable to that of cigarette smoking in middle-aged men) are likely to be useful in risk algorithms. It should be emphasised, however, that minor risk predictors in the overall population may still impart high risk in specific subsets, for example, due to the interaction of a gene with other genes and the environment (e.g., cigarette smoking).

Myocardial infarction is the most ominous complication of CAD. Although established risk factors of CAD predict MI as well, not all patients afflicted with CAD will suffer from MI, suggesting that additional factors that promote progression from a stable to an unstable atherosclerotic plaque with plaque rupture and thrombosis are involved. Most genetic association studies of CAD and MI have focused on a single gene, thus ignoring their multifactorial pathophysiology by excluding the remainder of the genome, as well as environmental factors. However, recent advances in high-throughput genomic technology made it possible to study multiple gene polymorphisms. The GeneQuest study analysed 72 SNPs within 62 genes in 352 cases with familial premature MI and in 418 controls in a population of white Americans, identifying a potential association with three variants of the thrombospondin gene family. Another 112 polymorphisms in 71 candidate genes were analysed in a Japanese study of 2819 cases with MI and 2242 controls, identifying a potential association with SNPs in the...
The prevalence of MI remains unknown. Recently, the European and American Societies of Cardiology redefined the laboratory definition for MI, which now includes plasma troponin levels. Although this definition will pick up smaller MIs, clinically silent MIs are frequent in advanced CAD and it is only the tip of the iceberg that we realise clinically. Thus, in case-control studies of MI, we should keep in mind that cases refer to a phenotype (i.e., clinically diagnosed MI) that only reflects a subset of all MIs. Consequently, identification of appropriate controls remains a critical issue. Tobin and coworkers identified 8 genes associated with the metabolic syndrome (see Table 3 in Bugert et al.11). Thus, validation will require large databases of carefully defined clinical phenotypes and accurate genotyping data, along with long-term follow-up for key clinical endpoints in order to assess the clinical relevance of such genetic variation.

The study by Tobin and coworkers seems to provide more questions than answers, following the general pattern of studies on genetic associations of common diseases. For most polymorphisms, therapeutic implications in complex diseases are a long way off. Thus, validated genetic approaches to the prevention and treatment of common diseases are unlikely to be available by 2010. Instead, we currently are witnessing a proliferation of pseudoscientific approaches involving direct-to-consumer marketing of genetic tests and genetic testing sites on the Internet. In the United Kingdom, for instance, a chain of health stores began to sell a series of nine genetic tests in combination with a lifestyle questionnaire, which allegedly offered "genetically tuned" advice. Not only are these tests of little usefulness, if any, but they can also cause anxiety or false reassurance.

We are entering a new era of genetic association analyses for complex diseases. High-throughput genotyping makes it possible to test as many as 1 million genetic variants in a given individual using recently developed microchips. Future studies need to address evolutionary relations among haplotypes and tackle the issue of gene–gene and gene–environment interaction in order to bring us closer to genomic medicine. However, these approaches will come with new challenges. Therefore, at the moment, studies like the one reported by Tobin et al.7 are very important and useful, as long as we keep in mind their limitations.

References


