

The Future of Medicine: Molecular Medicine in a Changing World

Tıbbın Geleceği: Değişen Dünyada Moleküler Tıp

Molecular genetics is beginning to enhance diagnostics, the prediction of genetic disease, our understanding of development, and promises to identify important alleles at loci that predispose towards the development of common conditions such as coronary heart disease, stroke and cancer.

Coronary artery disease (CAD) is a multifactorial disease caused by various genetic and environmental factors involved in the pathogenesis of atherosclerosis and its thrombotic complications (1). The renin-angiotensin system (RAS) plays a central role in cardiovascular homeostasis. Angiotensin is a key peptide of the RAS. Numerous studies in the past 12 years have demonstrated that the pharmacological inhibition of angiotensin-converting enzyme (ACE) which converts angiotensin I to angiotensin II and inactivates bradykinin and tachykinins, improves the outcome in patients with several cardiovascular disorders (2).

The human ACE gene is found on chromosome 17 and a polymorphism has been identified in which the presence (insertion, I allele) rather than the absence (deletion, D allele) of a 287 base pair (bp) fragment is associated with lower serum level and tissue ACE activity.

The ACE gene polymorphism was first reported by Rigat et al. in a study that addressed the role of the ACE gene in the genetic control of plasma ACE levels (3).

One of the first studies showing the DD genotype association with increased risk of myocardial infarction (MI) was reported by Cambien et al. in 1992 (4). The DD genotype was found at significantly higher frequency in subjects with MI compared to controls. This report stated that the presence of the DD genotype is a risk factor involved in the pathogenesis of atherosclerosis, thrombosis and vasoconstriction (4). Other case-controlled studies confirmed these findings and even found that the DD genotype was an independent risk factor for MI (5-9).

The study by Nacak et al. (10) did not confirm the possibility that the ACE DD genotypes may be associated with predisposition to CAD in the South-Eastern Anatolian population but there was a weak relationship between the II genotype and CAD. The II genotype seemed to be an independent protective factor for CAD in the South-Eastern Anatolian population.

In contrast to the numerous studies reporting positive disease associations of ACE polymorphism with cardiovascular disease, several large-scale studies and a recent meta-analysis did not confirm these findings (11-16). Negative findings in disease association studies and meta-analyses underline the important concept that multiple interacting factors, like mainly genetic and environmental, contribute to the development of CAD and MI. In this respect, the risk for CAD and MI can be relevant to interaction between different genetic polymorphisms and mutations. Future studies should not only have sufficient sample size to detect small genetic effects, but should also consider gene-gene interactions and interaction between genetic background and other environmental factors. The small number of polymorphisms in the RAS genes that appear to be clinically significant and may change dramatically in the future years with completion of the Human Genome Project. This project will set the stage for complex genetic profiling and risk stratification in patients with cardiovascular disease. Dr. Francis Collins (Director of the National Human Genome Research Institute) said, "I would be willing to make a prediction within 10 years, we will have the potential of offering any of you the opportunity to find out what particular genetic conditions you may be at increased risk for based upon the discovery of genes involved in common illnesses like diabetes, hypertension, heart disease, and so on."

In conclusion, a statistical relation can be found in most subsets of patients. A relation between genotype and phenotype is usually found before development of disease, but it remains difficult to confirm

this relation after the development of the disease because of complexity of genetic interactions. The actual presence of such a relation and the pathophysiological value and the use of genotyping patients for individualised treatment therefore remain obscure. Molecular cardiology is changing by our concepts of cardiovascular development, disease etiology, pathophysiology and therapy at a rapid pace. New developments in molecular biology will help direct research in human disease etiology towards its genetic basis.

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