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Association of Certain Gene Polymorphisms with the Risk of Atrial Fibrillation in Patients with Ischemic Heart Disease

Nasyrova Zarina Akbarovna
Associate Professor of the Department of Internal Medicine No. 2 and Cardiology, Samarkand State Medical University, Samarkand, Uzbekistan

Annotation: There is increasing evidence that gene-environment interactions play an important role in genetic studies of complex diseases. The renin-angiotensin system is a major regulator of blood pressure and cardiovascular homeostasis. AGT is an important component of the renin-angiotensin system. AGT is a precursor of angiotensin II, which causes acute vasoconstriction and stimulates proliferation of vascular muscle cells and cardiomyocytes. Many studies have evaluated the association of AGT T174M polymorphism with CHD risk, but the above observed associations consisted of a small number of samples, and the results may reflect chance observations rather than true associations.

Keywords: atrial fibrillation, genetic study, renin-angiotensin system, human angiotensinogen.

Introduction. Coronary heart disease (CHD) remains a major cause of adult morbidity and mortality in both Europe and North America [1,2,15]. It is projected that eight million additional people may develop CHD by 2030, a 16.6% increase from 2010 in the United States [2,4,11]. In 2008, the overall mortality rate for CHD was 122.7 per 100,000 population. From 1998 to 2008, the annual IBS mortality rate decreased by 28.7% and the actual number of deaths decreased by 11.9%. In the United States, the mortality rate was 161.7 for white men and 183.7 for black men, and the death rate was 91.9 for white women and 115.6 for black women [3,5,9,14]. The study showed that pre-exposure risk factors were common among individuals who developed coronary heart disease. About 90% of patients with coronary heart disease had previous exposure to at least one of the major risk factors, which include high total blood cholesterol or current use of cholesterol-lowering medications, hypertension or current use of blood pressure-lowering medications, current smoking, or clinical report of diabetes [4,20,22].

There is increasing evidence that gene-environment interactions play an important role in genetic studies of complex diseases. Human angiotensinogen (AGT) is produced by the liver and converted to angiotensin I by the action of renin. Angiotensin I is then converted to angiotensin II, leading to myocardial hypertrophy, fibrosis, and vasoconstriction. The AGT gene is located at the lq42-43 site and consists of five exons [5,6,12]. The substitution of threonine for methionine at amino acid 174 is a common polymorphism called T174M (rs699), denoting the T and M alleles, respectively [6,13,21]. During the last decade, the T174M polymorphism of the AGT gene has been investigated for its association with the risk of developing CHD. Tiret et al [7,9,14] were the first to study the association between AGT T174M polymorphism and myocardial infarction (MI), the study population included 630 patients and 741 controls. The results showed that the distribution of T174M genotype was not different between the patient group and control group, and showed no significant association between T174M and the risk of MI [7,16,19]. Later, several studies, but not all, confirmed the association between AGT T174M polymorphism and predisposition to CHD**.** The renin-angiotensin system is one of the major regulators of blood pressure and cardiovascular homeostasis. AGT is an important component of the renin-angiotensin system. AGT is a precursor of angiotensin II, which causes acute vasoconstriction and stimulates proliferation of vascular muscle cells and cardiomyocytes. Many studies have evaluated the association of the AGT T174M polymorphism with CHD risk, but the above observed associations consisted of a small number of samples, and the results may reflect chance observations rather than true associations. A previous meta-analysis in 2007 by Xu et al . investigated

the association between T174M and CHD risk in sixteen studies, which did not confirm an association between T174M polymorphism and CHD susceptibility. However, there was no stratified analysis to assess the association between the T174M/M235T polymorphism and CHD risk. Consequently, ethnicity or differences in the end point of assessment may have influenced the results. The results of many meta-analyses have shown that the T174M polymorphism may be a potential risk factor for CHD in Caucasians. However, the results of Begg's funnel plot test showed that there was no publication bias, and the data led us to conclude that heterogeneity was strongly associated with the end point of CHD. In addition, we should point out that the T174M polymorphism may be associated with Caucasian patients with coronary stenosis rather than MI. The results are in agreement with recent studies reporting that the occurrence of MI and coronary atherosclerosis is due to different genetic variants. In a subgroup analysis by ethnicity, no significant association was found between the T174M polymorphism and susceptibility to CHD in Asians, suggesting a possible role for ethnic differences in genetic background and environment. Because the number of eligible studies in this meta-analysis of T174M polymorphism was small, the results still need further investigation [18,20,22].

The mechanism of how the AGT T174M polymorphism is associated with the risk of coronary stenosis is still unclear. It has been shown that serum AGT levels are higher in subjects carrying the T allele. AGT interacts with renin to produce angiotensin II. Angiotensin II activates vascular cell apoptosis, contributing to vascular remodeling and cardiomyocyte loss during ischemia-reperfusion. In addition, angiotensin II has been shown in both human and animal models to be involved in the development of cardiomyocyte hypertrophy, cardiac fibrosis, and modulation of cardiac fibroblast growth and collagen synthesis. In addition, non-equilibrium linkage of M235T and T174M in exon 2 of the AGT gene may synergistically increase the risk of CHD. This evidence suggests that the T174M polymorphism may play an important role in the development of coronary stenosis [17,20,23].

Conclusions: thus, it should be noted that the results of many studies indicate a significant association of AGT T174M polymorphism with the risk of coronary stenosis in Caucasians. However, further studies of gene-gene and gene-environment interactions should be taken into account.

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