SCIENCE FOR SURGEONS

An overview of renin angiotensin aldosterone system genetics and cardiovascular disease

Fazli Rabbi Awan[1] and Misbah Hussain[1]

[1]Diabetes and Cardio-Metabolic Disorders Laboratory, Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering (NIBGE), Faisalabad, Pakistan

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Correspondence:
Dr. Fazli Rabbi Awan, Diabetes and Cardio-Metabolic Disorders Laboratory, Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering (NIBGE), Jhang Road, Faisalabad, Pakistan
Email: awan.fr@gmail.com | Tel: +92-334-4117448| Fax:+92-41-9201472

Dr Fazli Rabbi Awan, MSc,MPhil, DPhil (Oxon), the main author of this paper, is Principal Scientist, at Diabetes and Cardio-Metabolic Disorders Laboratory of Health Biotechnology Division, at National Institute for Biotechnology and Genetic Engineering (NIBGE). He also holds the academic position of Adjunct Associate Professor (Health Biotechnology) at Pakistan Institute of Engineering and Applied Sciences (PIEAS), Islamabad. He has made valuable contributions in the field of Genetic Engineering and Biotechnology and has published many high quality research papers in this field. From the forum of NIBGE, Dr. Fazil Rabbi Awan has collaborated with Faisalabad Institute of Cardiology for conducting several research projects in field of cardiovascular diseases.

ABSTRACT

Cardiovascular diseases result owing to various environmental and biological factors. Hypertension is the most common and detrimental metabolic risk factor for cardiovascular disease, which damages the endothelial cells of blood vessels and the heart. Renin angiotensin aldosterone system (RAAS) is a key pathway that maintains blood pressure homeostasis. Variants of RAAS genes (renin, *ACE*, *AGT*, *AGT1R*, *AGT2R* and aldosterone synthase genes) determine its activity level and influence the risk of cardiovascular disease. For example, DD genotype of *ACE* (I/D) polymorphism increases the plasma activity of ACE and elevates blood pressure. Similarly, T allele of *AGT* (M235T) and C allele of *AGT1R* (A1166C) gene variants substantially increase the risk of cardiovascular diseases. Moreover, these variants also influence the efficacy of antihypertensive drugs. However, the results of association between RAAS gene polymorphisms and various pathologies and response to antihypertensive drugs are still conflicting and require detailed studies in the target populations.

Key words: Cardiovascular diseases, Hypertension, RAAS, ACEi, ARBs

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading causes of deaths worldwide as 31% of global annual deaths are attributed to CVDs. Since last decade, CVD related morbidity and mortality has been reduced in high-income countries while an increase has been observed in low and middle-income countries. South Asians including Pakistani population is more prone to coronary heart disease (CHD).

Various metabolic, environmental and dietary

risk factors have greatly increased the CVD prevalence among several populations e.g. Pakistan, India, Bangladesh, Sri Lanka, and China etc. Among these risk factors, metabolic factors need special attention as their regulation is more critical and important than other modifiable risk factors. Hypertension is the most prevalent metabolic risk factor for CVDs. A recent study reported that 41% of adult Pakistani population is hypertensive (1). Hypertension is a heterogeneous pathological condition because in most of the patients it remains asymptomatic and silently damage blood vessels and heart tissues which make it a strong risk factor for CVDs. Various endogenous and exogenous factors like high salt intake, physical inactivity, smoking, vasoconstriction, sodium reabsorption, increased blood fluid volume and aldosterone release are responsible for increased blood pressure. The endogenous hypertension promoting factors are mainly controlled by a physiological pathway known as renin angiotensin aldosterone system (RAAS).

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS) AND ITS GENETIC VARIANTS

The RAAS plays a critical role in blood pressure regulation and maintenance of blood electrolyte and fluid volume. As the name indicates, RAAS gets activated with the secretion of renin from kidneys. Renin cleaves the liver secreted angiotensinogen (AGT) and converts it to angiotensin I. Angiotensin converting enzyme (ACE) further cleaves angiotensin I and forms an octapeptide, angiotensin II (Ang II), which is the main bioactive component of RAAS. Ang II can bind to two types of receptors: angiotensin II type 1 receptor (AGT1R) and angiotensin II type 2 receptor (AGT2R), mostly it binds to AGT1R (2). Ang II-AGT1R axis activates cellular signaling pathways leading to vasoconstriction, salt reabsorption, aldosterone production, leukocyte adhesion to vascular wall, smooth muscle cell proliferation and migration etc. (Figure 1).

In hypotensive conditions, Ang II-AGT1R plays an important role in increasing blood pressure to maintain the required blood pressure levels. However, over-activation of AGT1R stimulated cellular signaling pathways can increase hypertension, CHD and other CVDs.

Several studies have reported that genetic variants in the RAAS genes are associated with the increased risk of coronary heart disease, myocardial infarction etc. (3-5). Till date, several

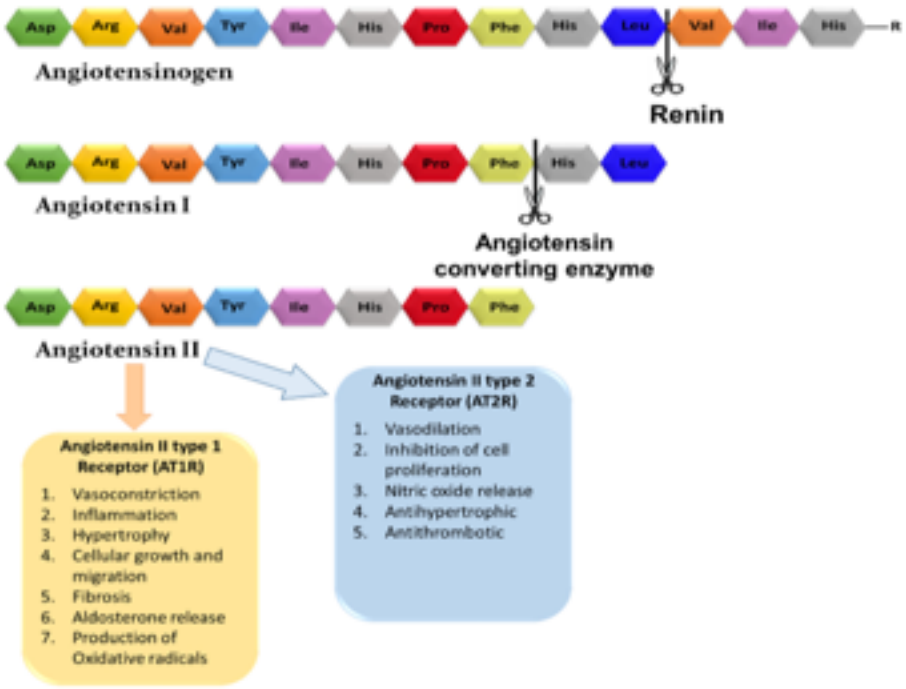

Figure 1: An overview of renin angiotensin

polymorphisms have been explored for their association with CVDs and its risk factors. Among those polymorphisms, Insertion/ Deletion (I/D) polymorphism of ACE, M235T of AGT and A1166C polymorphism of AGT1R gene are most widely studied polymorphisms for their association with hypertension and CVDs.

It was previously reported that individuals carrying DD genotype of ACE (I/D) polymorphism have higher levels of plasma ACE, which is a stimulator of increased Ang II production (6). Our recent study conducted on 100 hypertensive Pakistani patients also favored this finding by showing that DD genotype is associated with increased systolic blood pressure (7). Another study from our group with increased sample size showed that individuals carrying ACE II genotype are at an additional two fold higher risk of CVDs in diabetic subjects as compared to the carriers of DD and ID genotype (8). Studies involving other RAAS gene polymorphisms present some conflicting results.

Population heterogeneity exists in the association studies of RAAS gene variants. Malaysian (9),Chinese (10, 11), South Indian (12), Tunisian (13) and Egyptian (14) population showed that T allele of AGT M235T polymorphism increases the risk of hypertension and CVDs while Mongolian (15), Caucasian (16), Lebanese (17) and Indian population (18) report no association. Large studies with longer follow up period should be conducted to resolve such conflicts.

PHARMACOGENETICS AND CARDIOVASCULAR DISEASES

Due to the direct role of RAAS in increasing the risk of cardiovascular disease (CVD), RAAS blockades are prescribed to cardiac patients to improve their health outcomes. Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), β-blockers and diuretics are more commonly recommended to cardiac patients due to their beneficial effects in reducing blood pressure and improving heart health.

Among these RAAS blockades, ACEi and ARBs are prescribed as first line therapy to treat hypertension. However, the effects of the drugs vary widely from population to population. In Black Africans, the ACEi and ARBs do not respond well and fail to attain required blood pressure due to low plasma renin levels in Africans. While all other populations respond to these drugs adequately; however, strong inter-individual drug response variability also exists.

The underlying reason for variable drug efficacy could be the differences in genetic makeup of populations and individuals. The efficiency of long-term prophylactic treatment of hypertensive patients with aforementioned drugs will increase exponentially if clinicians could know that who will respond better to the drugs. It will also help in reducing the adverse effects of drug. The only solution for this problem is pharmacogenetic studies which is a key to personalized medicines.

The ACE (I/D) and AGT (M235T, T174M) are most widely studied polymorphisms with respect to efficacy of ACEi and ARB in controlling blood pressure. These drugs directly affect the angiotensin II and block its pathological effects. ACEi stops the catalytic activity of ACE and reduce the circulatory levels angiotensin II while ARBs act as antagonist for angiotensin II and competitively inhibit the activation of AGT1R. It is a well-established that DD genotype of ACE gene increases the ACE plasma levels, but the effects of ACE (I/D) genotypes on drug response is non-conclusive. Some studies report that DD genotype favors the ACEi response (19, 20), while others report the association between II genotype and blood pressure reduction by ACEi (21, 22) and several studies came out with no effect of genotypes on ACEi therapy (23-25).

A 12-week follow-up study was conducted by our group to explore the effects of RAAS gene variants on ACEi and ARB efficacy. For this, 11 genetic polymorphisms in the RAAS were studied and no association was witnessed for RAAS gene variants and response to antihypertensive drugs. Even the genotype frequencies of AGT polymorphisms (M235T and T174M) were exactly same in responding and non-responding group. However, a weak association has been observed for ACE inhibition and aldosterone synthase gene (CYP11B1) polymorphisms (rs6387 and rs6410) (26). The possible reason for this weak association could be shorter follow-up period. Stimulation of aldosterone secretion from adrenal glands is one of the several functions of angiotensin II, the main target of ACEi and ARBs. Many studies have confirmed that short term treatment with ACEi and ARBs reduces the

aldosterone levels, while its levels increase back to baseline on chronic treatment, phenomena termed as aldosterone escape (27, 28). So, in long term prophylactic treatment with ACEi and ARB the aldosterone escape will be encountered. To overcome this problem, combination therapy with β-blockers is commonly prescribed. Although, it works well to achieve the adequate blood pressure levels, however it also doubles the adverse effects of drugs used. More studies with stringent criteria should be conducted to evaluate the precise association between RAAS gene polymorphisms and response to antihypertensive therapy. Research in that direction requires close collaboration between scientists and the clinical experts. Understanding the importance of this close collaboration NIBGE and Faisalabad Institute of Cardiology (FIC) are working together in several research projects. A Pharmacogenetics study of heart disease patients for the evaluation of drug efficacy in renin angiotensin aldosterone system (RAAS) pathway in currently being conducted and is likely to provide results of paramount importance. Similarly, genetic and bioinformatic analysis of inflammatory makers of atherosclerosis is also being done which may change the way we would do screening and diagnosis of ischemic heart disease.

CONCLUSION

Variations of RAAS genes directly affect the activity of RAAS bioactive components. These RAAS gene polymorphisms are associated with elevated blood pressure and increased risk of developing cardiovascular disease. Genetic variants also influence response to antihypertensive therapy, which warrant pharmacogenetic studies at the interface of genes and drugs in cardiovascular disease patients.

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