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Genetic Variants and Atherosclerosis

M. Seifi, A. Ghasemi, M. Khosravi, M. Salimi, S. Jahandideh, J. Sherizadeh, F. S. Hashemizadeh, and R. Khodaei

***Abstract*—**Atherosclerosis is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle) lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries.

***Keywords*—**Arterial blood vessels, atherosclerosis, cholesterol.

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I. Introduction

CORONARY artery disease (CAD), or narrowing of the coronary arteries due to atherosclerosis, remains one of the leading causes of morbidity and mortality worldwide. Atherosclerosis is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol (Figure 1). It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle) lipoproteins without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries [1]. Atherosclerosis is the main cause of CV disease, including ischemic stroke, CHD, and ACS [2-10]. The clinical course related to atherosclerotic changes may not be a gradual and progressive one; rather, patients may remain asymptomatic for years, with sudden death marking the first clinical manifestation [3]. Equally unpredictable is the onset of CV events, which have not correlated well with the commonly used Framingham risk status model. The majority of events are seen in patients categorized as low or intermediate risk of CHD based on the Framingham risk equation [3]. These data highlight the need for early diagnosis and treatment of subclinical disease. Advances in recent research have provided greater understanding of the underlying pathophysiology of atherosclerosis. Evidence now supports that atherosclerosis is a progressive, dynamic, inflammatory process, which can indeed be modified by preventive and therapeutic measures [7,8,11].

A. Ghasemi, M. Salimi, S. Jahandideh, J. Sherizadeh, F.S. Hashemizadeh, R.Khodaei are with Iran University of Medical Sciences, P. O. Box No: 1449614525, Tehran, Iran.

M. Khosravi is with Ahvaz University of Medical Sciences, P. O. Box No: 1449614525, Ahvaz, Iran.

M. Seifi is with Gifted & Talented Students Center, Medical Education & Development Center, Iran University of Medical Science, PO.BOX: 14155-5983, Tehran, Iran (corresponding phone: (98)21- 88058742 (Ext. 3116); fax: (98)21- 88058742; e-mail: morteza.seifi@iums.ac.ir).

A. Molecular Mechanisms Involved in Formation of Atherosclerotic Plaque

The atherosclerotic plaque or atheroma is the key feature in the development of atherosclerosis. Formation of atheroma lasts over decades, starting with early lesions which may occur in early adolescence. The velocity of progression depends on many factors, such as gender, genetics and some well recognized risk factors (e.g. hyperlipoproteinemia as mentioned below). Once initiated, the atheroma may remain stable for many years, causing only rarely symptoms such as stable angina pectoris or claudicatio. But some factors may lead to an unstable plaque, resulting in more grave or even fatal acute events such as myocardial infarction. In the initiation of atherosclerotic lesions, migration of mononuclear leukocytes is one key feature. This migration is mediated by several cytokines which are produced by the endothelial cells under certain influences [12]. Selectins are one family of those endothelial leukocyte adhesion molecules. One member of this family, namely P selectin, is thought to mediate rolling or transitory contact of leukocytes with the endothelium. It is found to be expressed in endothelial cells overlying human atheromas, but not in those of normal vessels [13]. Another important cytokine involved in leukocyte adhesion and immigration is vascular cell adhesion molecule 1 (VCAM-1). VCAM-1 is found to be expressed early at sites of atherosclerotic lesion formation in animal models [14]. After adhesion, leukocytes migrate into the artery wall directed by various chemoattractant chemokines. In experimental animals, macrophage chemoattractant protein-1 (MCP-1) seems to play an important role in this process [15]. Oxidized phospholipids are present in modified lipoproteins such as oxidized LDL and are a link between hyperlipidemia and local increase of adhesion molecules or cytokine expressions at sites of atherosclerotic lesions. Experimental data suggest that those modified phospholipids like lysophosphatidyl choline or palmitoyl oxovaleroylglycerophosphoryl choline are able to trigger expression of adhesion molecules and cytokines involved in plaque formation [16]. After the migration of leukocytes into the intima, they accumulate modified lipids and were transformed to foam cells. The receptor responsible

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for uptake of lipids is named scavenger receptor [17]. The production of mediators like platelet-derived growth factor (PDGF) [18], heparin-binding epidermal growth factor [19] and insulin-like growth factors by endothelial cells and by the mononuclear macrophages themselves mediate the accumulation of smooth muscle cells and of extracellular matrix macromolecules [20]. This process results in formation and growing of progressive atheroma. The stability of such a plaque is due to the composition and thickness of its fibrinous cap. The majority of acute coronary event result from a rupture of this protective cap. The most important factor contributing to the biomechanical strength of this cap are the interstitial forms of collagen. Main collagen production is made by the smooth muscle cells under influence of certain factors such as PDGF. Other factors like interferon gamma inhibit gene expression and protein synthesis in those cells [21]. Gamma interferon is produced by stimulated T cells, which are frequently found accumulating at sites of acute plaque rupture and thrombosis [22]. So the inhibition of collagen synthesis by mediators produced by activated T cells seems to be one key factor in transforming stable plaques to unstable ones. In addition, enzymes of the matrix metalloproteinase family (MMP) produced by activated macrophages may play an important role with proteolytic degradation of formerly produced collagen fibrils [23].

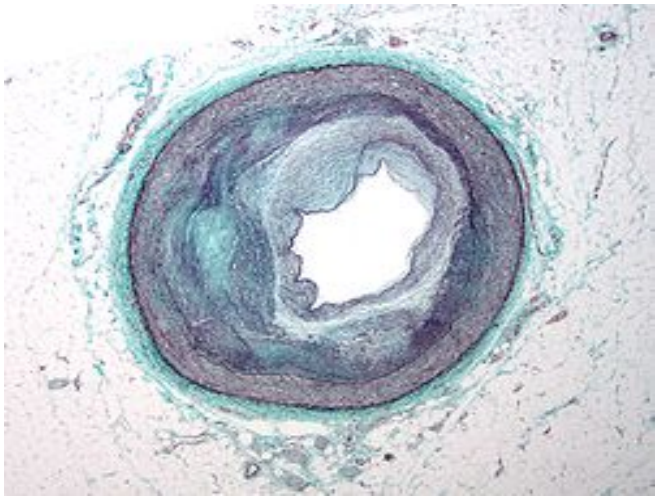


Fig. 1 Micrograph of an artery that supplies the heart with significant atherosclerosis and marked luminal narrowing. Masson's trichrome

B. Types of Plaque

The major constituents of atherosclerotic lesions are matrix proteins (including collagens, proteoglycans, elastin, etc), smooth muscle cells, macrophages and lipids [24]. However, the relative proportions of these components vary among different plaques. At one end of the spectrum are plaques rich in lipids and macrophages, which are commonly referred to as lipid rich plaques [25,26]. At the other end of the spectrum are plaques rich in matrix proteins and smooth muscle cells, which are referred to as fibrotic plaques [25,26]. Lipid rich plaques are prone to rupture, causing myocardial infarction. In comparison, fibrotic plaques are usually more stable but bulkier [25,26]. Although a patient may have more than one atherosclerotic plaque, an autopsy study of individuals with coronary artery disease showed that in 15% of the subjects all plaques were the fibrotic type, in 13% of the subjects all plaques were of the lipid rich type, and in the remaining subjects both types of plaque were present [27].

C. Physiologic Factors that Increase Risk

Risk factors that cause formation of plaque and increase occurrence of atherosclerosis are: Modifiable factors (eg. Diabetes, dyslipoproteinemia, an LDL:HDL ratio greater than 3:1, elevated serum C-reactive protein concentrations and etc), nonmodifiable factors (eg. Advanced age, male sex, genetic abnormalities and having close relatives who have had some complication of atherosclerosis), lesser or uncertain factors (eg. Being obese, postmenopausal estrogen deficiency, intake of trans fat, Chlamydia pneumoniae infection etc) and dietary risk factors [28].

II. Genetic Variants Related to Atherosclerosis

Although the plaque develops as a chronic inflammatory reaction, there is increasing evidence that DNA damage to cells within the lesion plays an important role in both atherogenesis and the behaviour of established lesions [29-31]. DNA damage ranges from 'macro' damage, including deletions or additions of whole chromosomes or parts of chromosomes, to 'micro' damage, which includes DNA strand breaks, mutations of single bases, modified bases (including oxidation) or DNA adducts. Several genetic variants have been examined in relation to atherosclerosis, more commonly by association than linkage analysis. Findings from the most widely studied variants are summarized, followed by a listing of variants only beginning to be explored in relation to atherosclerosis disease.

A. Matrix Metalloproteinase

The matrix metalloproteinases (MMPs), are a family of enzymes required for degradation of the extracellular matrix during embryo development, morphogenesis and tissue remodeling. MMPs degrade most of the extracellular matrixconstituents within atherosclerotic plaques [32]. It is well accepted that MMPs are key players in most vascular diseases and a similar elucidation of the spectrum of expression and specific roles has to be effected before a therapeutic opportunity can be clearly identified [33-35]. MMPs have been implicated in intimal thickening, a repair response to damage of the walls of large arteries in human atherosclerotic pathologies, as well as in the subsequent plaque rupture. Hence, the concept of 'good' and 'bad' MMPs can be invoked in cardiovascular disease as in cancer, but the existing data from animal model studies are not clear cut. Studies using MMP gene knockout mice have indicated that MMP-2 and MMP-9 play key roles in cardiac rupture after myocardial infarction [36-42]. A recent study showed that MT1-MMP (MMP-14) is increased after ischemia-reperfusion [43]. TIMP-3 deficiency in mice disrupted matrix homeostasis and caused spontaneous left ventricular dilation, cardiomyocyte hypertrophy and contractile dysfunction [44].

Open Science Index, Medical and Health Sciences Vol:3, No:9, 2009 publications.waset.org/14682/pdf

A critical role of MMP-2 and MMP-9 has been also shown for the development of abdominal aortic aneurysm using MMP gene deletion mice [45]. Recent studies on atherosclerotic plaque stability using a series of apoE/MMP double knockout mice have indicated that MMP-3 and MMP-9 have protective roles by limiting plaque growth and enhancing plaque stability, but MMP-12 promotes lesion expansion and destabilization [46]. Chase and Newby [47] have proposed that multiple steps of MMP gene induction occur in vascular pathologies due to the progressive recruitment of different cell types and inductive factors during different phases of the disease. A widening spectrum of MMPs, starting with MMP-2 and MMP-9, leading to MMP-1, MMP-12 and MMP-14, followed by MMP-3, MMP-11 and MMP-13 ultimately leads to a transition from matrix turnover to matrix destruction. An association between the MMP3 5A/6A promoter polymorphism and atherosclerosis was first described in 1995: the 6A6A genotype was associated with greater progression of coronary atherosclerosis [48]. Functional studies showed that the 6A allele was associated with twofold lower transcriptional activity [49]. Several investigators have used the clinical end point of coronary atherosclerosis or its progression, and >6000 people have been included in such analyses. The 6A6A genotype was associated with a greater progression of CAD after angioplasty [50]. In a study we examined 190 patients with coronary artery stenosis and 200 controls and indicated that there is a significant association between 6A/6A genotype MMP3 gene polymorphism and Extent of Coronary Atherosclerosis [51].

B. Paraoxonase

The paraoxonase gene family consists of three members of PON1, PON2, and PON3, located adjacent to each other on the long arm of chromosome 7 [52]. All 3 gene products protect low density lipoprotein (LDL) from oxidation, at least in vitro [53]. paraoxonase 1 and 3 (PON1 and PON3) associated with the circulating high density lipoprotein (HDL) particles but paraoxonase 2 (PON2) that expressed widely in a number of tissues including the liver, lungs, brain and heart dose not appear to be associated with HDL [54]. PON1 hydrolyzes organophosphates such as paraoxone, carbomates, and nerve gases, therefore it was initially investigated in the field of toxicology [55]. PON1 has been shown to protect LDL against oxidative modification in vitro by preventing accumulation of lipid peroxides [56]. Peroxidation of LDL is recognized to plays central role in atherogenesis [57]; therefore recently PON1 has been implicated in the pathogenesis of atherosclerosis and cardiovascular disease (CVD). Several studies have suggested that either paraoxonase-1 (PON1) is associated with oxidative stress [58,59]. The oxidative modification of low-density lipoprotein (LDL) is an important element in the development of atherosclerosis [60]. Numerous studies suggest that oxidative modification of LDL in the arterial wall initiates development of foam cell-laden fatty streaks, which are believed to cause atherosclerosis [61]. Recent evidence suggests that high-density lipoprotein (HDL) inhibits oxidation of LDL and thus, may protect against risk of CAD [62]. Paraoxonase-1, an HDL-associate enzyme, has been shown to be responsible for this antioxidative property of HDL [63]. Paraoxonase-1 is a 44-kD Ca+2–dependent enzyme that is associated with apolipoprotein (Apo) A1 and Apo J on HDL [64,65]. The PON1 gene has 2 common polymorphisms in the coding region, which lead to a glutamine→arginine substitution at position 192 and leucine→methionine substitution at position 55. These sites are identical to positions 54 and 191, when alanine is defined as the N-terminal residue. The variants are designated PON1 M/L55 and R/Q192 [66,67]. Only 2 studies examined the PON 2 S311C polymorphism and found no relationship with carotid atherosclerosis [68,69]. Examination of 2 additional promoter polymorphisms, as well as a haplotype comprising polymorphisms at -162/-108/55/192, failed to detect any association with stenosis cases[70]. Of 13 studies considering the PON 1 192 polymorphism separately or jointly with PON 1 55, 10 showed no association with PON 1 192 considered alone [68,69,70,71,72-77], although 1 of these showed IMT to be higher in subjects homozygous for the PON 1 55 L and PON 1 192Q alleles compared with LL/RR and MM/QQ subjects [77], and another showed the PON 1 192RR genotype to be more common than QQ in stenosis cases but only after adjustment for PON activity level [76]. This report was subsequently refuted in an expanded sample from the same authors, who found no association regardless of adjustment for PON activity [70]. An eleventh study showed higher IMT in RR homozygotes than Q allele carriers [78]; the twelfth showed plaque to be more frequent in PON 1 192R carriers with high levels of high-density lipoprotein, but no difference in plaque by genotype in subjects with low levels of high-density lipoprotein [79]. The thirteenth showed the R allele to be more frequent in older persons with moderate versus no atherosclerosis [80]. It has been shown that the PON1 R allozyme is less efficient at retarding the oxidation of LDL than is the Q allozyme because of the decreased hydrolysis of lipid peroxides by he R allozyme [81,82]. This finding may explain why in our study the PON1 R allele has been found to be present at an increased frequency in coronary artery disease (CAD).This finding is accordance to some studies that performed in different population and coronary artery disease; as in 81 stroke patients who were compared with 2553 control subjects, PON1R was shown to be an independent risk factor for stroke [83]. Similarly in a case-control study of 139 CAD patients and 119 control subjects; RR genotype not only defined as an independent risk factor for CAD; but also as a factor that related with the severity of disease [84].

C. Apolipoprotein E

Apolipoprotein E, a key protein in the transport of cholesterol, has been a suspect in regard to the role played by genetic polymorphisms as risk factors for cardiovascular disease due to atherosclerosis, either as a result of variances in cholesterol transport among genotypes or by direct effect of the polymorphisms upon human atherogenesis [85-87]. Apolipoprotein (apo) ε is a member of the apolipoprotein gene family. Other members of this multigene family include apo A-I, apo A-II, apo A-IV, apo C-I, apo C-II, and apo C-III. The coding regions of these genes are composed of tandem repeats of 11 codons, which suggests that they have evolved through

Open Science Index, Medical and Health Sciences Vol:3, No:9, 2009 publications.waset.org/14682/pdf

duplications of a primordial gene[88]. While there are rare variants, it is the polymorphism with its three alleles, *ε2, *ε3, and *ε4, that has been studied in relation to cardiovascular disease. From these alleles arise six phenotypes; their ranking from most to least common is generally 3/3, 4/3, 3/2, 4/4, 4/2, and 2/2 [89]. Apo E helps to stabilize and solubolize lipoproteins as they circulate in the blood. In general, the role of apolipoproteins in lipid metabolism includes maintaining the structural integrity of lipoproteins, serving as cofactors in enzymatic reactions, and acting as ligands for lipoprotein receptors. Apo E is critical in the formation of very low density lipoprotein (VLDL) and chylomicrons. compared with carriers of the *ε3 or *ε4 allele, carriers of the *ε2 allele are slower to clear dietary fat from their blood [90]. The difference in uptake of postprandial lipoprotein particles results in differences in regulating hepatic low density lipoprotein (LDL) receptors, which in turn contributes to genotypic differences in total and LDL cholesterol levels [89,91-95]. High levels of LDL cholesterol have been associated with increased risk of coronary heart disease (CHD). Sing and Davignon demonstrated that 8.3 percent of the total variance for LDL cholesterol is accounted for by the apo ε gene locus [96]. Apo ε contributes more to normal cholesterol variability than any other gene identified thus far in cholesterol metabolism [96]. In a population- based study Venkutaramana et al [97] reported that the allele frequencies in Indian population 85%-92% for ε_3 allele, 3.9% for ε_4 allele and 3.5% for ε_2 allele. In a study [98] we indicated that Apo ε allele frequencies in the control group of Tehran population are 34%, 34% and 32% for ε_4, ε_3 and ε_2 respectively which are not comparable with the study of Venkutaramana et al and others [97]. The reasons for these discrepancies could be genetic heterogeneity and gene environment interactions in different ethic population. It is well known that the ε_4 allele of Apo E is associated with increased prevalence of arthrosclerosis and cardiac heart disease (CHD) [99,100]. However there are controversial results concerning the association between Apo E genotypes and some cardiovascular risk factors. Some studies have suggested that high blood pressure may be associated with the presence of the ε_4 allele [101-103], while others have found its association with ε_2 allele [104]. However no association was found in few studies [104]. In our study we evaluated the distribution of Apo E genotype and alleles in angiogaraphically defined CAD patients and control subjects, and found these polymorphisms as risk factors for atherosclerosis [98].

D. Rennin-angiotensin System

The renin–angiotensin system, a two-enzyme cascade, plays an important role in the regulation of blood pressure, fluid balance, and electrolyte homeostasis [105,106] and in the pathogenesis of cardiovascular disease [107,108]. The initial enzyme, renin, cleaves its substrate, angiotensinogen, to angiotensin I, a decapeptide. Angiotensin I undergoes a second cleavage, mainly by tissue-bound angiotensin-converting enzyme and serine proteinase [109], to generate angiotensin II (an octapeptide), which via the angiotensin II type 1 receptor acts as a potent vasocon-strictor and aldosterone stimulating peptide. The angiotensin-converting enzyme also inactivates the nonapeptide bradykinin and blocks the tissue kallikrein system. Inhibition of the angiotensin-converting enzyme and antagonism of the angiotensin II type 1 receptor decrease blood pressure in hypertensive patients [110,111], and more importantly also prevent mortality and morbidity in patients with symptomatic or asymptomatic congestive heart failure [112-114], acute myocardial infarction [115], or diabetic nephropathy [116] Cloning of the human genes coding for the angiotensin-converting enzyme [117,118], an- giotensinogen [119], and the angiotensin II type 1 receptor [120] has led to the discovery of several polymorphisms, which may play a role as risk factors for cardiovascular disorders, such as hypertension, coronary heart disease, or cardiomyopathy. Among these genetic mutations, the angiotensin-converting enzyme gene deletionrinsertion (D/I) [121], angiotensinogen gene M235T [122], and the angiotensin II type 1 receptor gene A1166C[120] polymorphisms have been extensively investigated in various populations with a variety of cardiovascular disorders. Several other polymorphisms, in particular in the promoter region of the angiotensinogen gene, were also found to be associated with cardiovascular disease [123-127].

1. D/I polymorphism of the angiotensin-converting enzyme gene

In a landmark study, Cambien et al [128] observed an increased prevalence of the angiotensin-converting enzyme DD genotype in 610 Caucasian patients with a history of myocardial infarction. Subsequent studies found that the D allele was also associated with a higher risk of coronary heart disease [129,130], stroke [131,132], other atherosclerotic manifestations [133], or having a history of coronary heart disease [134,135]. One quantitative overview [121] demonstrated a strong association between atherosclerotic cardiovascular complications and the D/I polymorphism of the angiotensin-converting enzyme gene.

2. M235T angiotensinogen gene polymorphism

Several studies [136-138] demonstrated a significant association between coronary heart disease and the M235T polymorphism. However, in 12 studies combined, the T allele was not associated with atherosclerotic cardiovascular complications [122]. The pooled excess risk of 17%(P=0.08) in TT vs. MM homozygotes did not exceed the threshold of statistical significance in nine reports on coronary heart disease, including myocardial infarction. Similarly, for stroke and various other atherosclerotic manifestations, such as restenosis after angioplasty or the presence of atherosclerotic lesions [139,140], there was no excess risk in TT homozygotes compared with MM homozygotes.

3. A1166C polymorphism of the angiotensin II type 1 receptor gene

At least three studies observed synergistic effects of the angiotensin-converting enzyme D/I and the angiotensin II type 1 receptor A1166C polymorphisms on the risk of myocardial infarction [141] or coronary heart disease [142-143]. In a case-control study of 613 myocardial infarction cases and 723

age-matched population controls [141], the odds ratio associated with the angiotensin-converting enzyme DD genotype was 1.05 (95% CI 0.75–1.49) in subjects without the C allele of the angiotensin II type 1 receptor gene, 1.52 (95% CI 1.06–2.18) in AC hetero- zygotes and 3.95 (95% CI 1.26–12.4) in CC homozygotes(test for trend P<0.02).

III. Other Polymorphisms

Genetic variants related to hemostatic and inflammatory factors, interleukins and immune response [144-152], platelet receptors [153-160], and oxidative pathways [161-163], have also been studied sporadically. Associations with hemostasis-related variants have generally been absent [164-166] or present only in subgroups [153,167]. The Marburg I variant of factor VII activating protease and factor V Leiden, however, have been shown to be more frequent in those with plaque progression [168], whereas the β-fibrinogen C148T polymorphism in the homozygous TT form was associated with higher plaque score [168], although none of these associations was replicated in a large sample from the Framingham Heart Study [154].

IV. Conclusion

There is much to be learned regarding the genetic contribution to the observed phenotypic variability of atherosclerosi. Several questions that require answers include the following: To what extent do polymorphisms in relevant genes account for the observed variability in the phenotypic expression of pathologies that cannot be accounted for by risk factors alone, and what are their frequencies in populations? How do genetic differences alter the response to treatment strategies?

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Open Science Index, Medical and Health Sciences Vol:3, No:9, 2009 publications.waset.org/14682/pdf

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