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Mechanisms of Disease: Novel Polymorphisms in Coronary Artery Disease

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1. Introduction

Coronary artery disease (CAD) is one of the most common cardiovascular diseases and has a high incidence of morbidity and mortality. CAD is a major public health problem in developing and developed countries and its increasing prevalence is a cause of considerable concern in the medical community worldwide (He et al., 2005). CAD involves genetic and environmental factors and their interaction with each other. Traditional risk factors account for at most one-half of the prevalence of CAD (Zdravkovic et al., 2002). Despite attempts to establish the molecular and genetic determinants that could account for variations in CAD (Zdravkovic et al., 2002), the etiology and complex multigenic basis of atherosclerosis is still not completely understood.

Completion of the sequencing of the human genome was a monumental achievement (Venter et al., 2001). Molecular researchers now take for granted the information provided by the sequence, however the clinical applications are not immediately obvious. A limitation of the Human Genome Project was that it produced only a single "reference" sequence. But in order to identify new disease causing mechanisms and cures for disease, we need to go beyond the "reference" and characterize the differences between our genomes, and in turn the effect that these differences have. The Human HapMap consortium (Frazer et al., 2007) and recent genome-wide association studies (GWAS) have set out to capture the interindividual differences that are associated with disease processes, including coronary artery disease.

The association between genetic variations and CAD have been reviewed in several previous manuscripts (Lanktree et al., 2008), but in our knowledge so far there has been no study in the field of association between novel gene variations and CAD; therefore we focused on introducing some novel polymorphisms and their relationships with CAD.

2. Genetics of coronary artery disease

2.1 Genetic architecture of CAD

The success of CAD gene mapping is dependent on its genetic architecture which refers to the number of disease genes that exist, their allele frequencies, the risks that they confer, and

the interactions between multiple genetic and environmental factors (Wright & Hastie, 2001; Reich & Lander, 2001). Although the total genetic contribution to CAD risk can be quantified, the determination of the size and number of contributing effects is impossible without identifying all CAD susceptibility genes. The multiple risk factors for CAD themselves have their own genetic architecture. The heritabilities of some of the risk factors for CAD are considerable - total cholesterol (40 to 60%), HDL-cholesterol (45 to 75%), total triglycerides (40 to 80%), body mass index (25 to 60%), systolic blood pressure (50 to 70%), Lp(a) levels (90%), homocysteine levels (45%), type 2 diabetes (40 to 80%), fibrinogen (20 to 50%) (Lusis et al., 2004). Also, as CAD is rare before the age of 50 yr, it is unlikely to have an effect on reproductive success and hence less likely to have been subject to direct evolutionary selection pressure. Variants that confer susceptibility or protection for CAD might therefore have evolved neutrally in the past, and so could present at a wide range of frequencies.

This is the basis of the Common Disease/Common Variant (CDCV) hypothesis which holds that the genetic variants underlying complex traits occur with a relatively high frequency (>1%), have undergone little or no selection in earlier populations and are likely to date back to >100,000 years ago (Lander et al., 1996).The other competing model is the Common Disease Rare Variant hypothesis, with an inverse relationship between the magnitude of genetic effect and allele frequency (Pritchard et al., 2001). This model argues that diseases are common because of highly prevalent environmental influences, not because of common disease alleles in the population (Wright & Hastie, 2001). A review of candidate gene associations and recent genome wide association study results support the importance of common alleles in CAD. At odds with this, rare allelic variants of three candidate genes (ABCA1, APOA1, LCAT) that influence HDL levels, were jointly found to make a substantial contribution to the population distribution of HDL levels (Cohen et al., 2004; Frikke-Schmidt et al., 2004). The most likely scenario would be that the allelic spectrum of the disease variants is the same as the general spectrum of all disease variants. Under this neutral model, although most susceptibility variants are rare with minor allele frequencies (MAF) <1 per cent, variants with MAF>1 per cent would account for more than 90 per cent of the genetic differences between individuals. It is plausible that these common variants might contribute significantly to those common diseases in which susceptibility alleles might not be under intense negative selection.

2.2 Linkage and association studies

The 2 general types of studies that evaluate the relation between gene polymorphisms and disease are linkage analysis and association studies. Linkage analysis investigates the cosegregation of polymorphic DNA markers with inheritance of disease in families and has been highly successful in the detection of monogenic disorders. However, it is a tedious and complicated undertaking in the investigation of polygenic diseases such as CHD. Association studies provide an alternative method for dissecting genetically complex diseases and typically use the candidate gene approach for their investigation. Based on the known pathophysiologic characteristics of a disease, assumptions are made about the genes involved in its processes and the hypothesis of the association of these genes with the disease is then tested. For a disease such as CHD it makes sense to analyze genes that contribute to lipoprotein metabolism, blood pressure, and to diseases such as diabetes mellitus, among others.

This approach is more directed than is the genome-scan linkage approach, but it is limited by our incomplete knowledge of disease mechanisms and thus may miss important causative genes. It is worth noting that whereas in linkage analyses "disease" alleles are tracked in families, genetic association is a phenomenon of populations and association studies compare populations of subjects with and without the disease of interest (Bernhard et al., 2000).

2.3 Linkage studies

Previous methods for determining genetic linkage of a complex disease relied chiefly upon the technique of genome wide scanning of microsatellites (short tandem repeat sequences). This required the laborious selection of hundreds of families, particularly sib pairs with MI or CAD. Using around 400 microsatellite markers distributed evenly across the genome, the goal was to identify a significant linkage peak defined by a logarithm of odds ratio (LOD) greater than 3.5 corresponding to a $p<10\text{-}6$ indicating a gene that is in linkage disequilibrium (LD) near or even within the microsatellite region. However, identifying disease causing genes interspersed within microsatellites has proved to be quite difficult and studies from different centers reported varying results - Finland (2q21.2-22 and Xq23-26) (Pajukanta et al. 2000), Germany (14q32.2) (Broeckel et al., 2002), Iceland (13q12-13) (Helgadottir et al., 2004), US (1p34-36 ,3q13 and 5q31)(Hauser et al., 2004) and UK (2p11, 17p11-17q21) (Farrall et al., 2006; Samani et al. 2005). Genomic regions identified in the published linkage studies as being correlated with CHF are largely non-overlapping, suggesting genetic and/or phenotypic heterogeneity. Two genes, *ALOX5AP* and *MEF2A*, have been identified by fine mapping studies following the original linkage analysis. The Icelandic locus was replicated in population-based studies from Iceland and England, with different haplotypes of the *ALOX5AP* gene (encoding 5-lipoxygenase activating protein) associated with CAD in the two countries, and the Icelandic haplotype was also associated with stroke in Iceland and in Scotland (Helgadottir et al., 2004; Helgadottir et al., 2005). MEF2A (myocyte enhancer factor 2A) a transcription factor expressed in coronary artery endothelium was identified by linkage analysis in a pedigree in which 13 members had CAD, nine of whom had MI (Wang et al., 2003).

2.4 Genome-wide association studies

Genome-wide association studies (GWAS) became possible after the publication of the International Haplotype Map Project (HapMap) (International HapMap consortium, 2005; International HapMap consortium, 2007) and the development of array-based platforms that enable the investigation of up to one million variants in cases and controls of a certain disease (or other phenotypic traits). The HapMap was a large collaborative project that described the frequencies of genetic variants with a minor allele frequency above 5% in four distinct populations: Han Chinese, Japanese, Black African from Nigeria, and Caucasian of European ancestryfrom the USA (International HapMap consortium, 2005; International HapMap consortium, 2007).

The first GWAS to be conducted under these modalities was a large case-control study by the Wellcome Trust Case-Control Consortium (WTCCC), in which 14,000 cases affected by 7 among the most common complex diseases (CAD, arterial hypertension, rheumatoid arthritis, Crohn's disease, bipolar disorder, and diabetes mellitus types I and II) were compared with a set of 3,000 healthy controls. (Wellcome trust case control consortium,

2007) The WTCCC study identified 24 genetic variants associated with at least one of these complex diseases and helped to clarify key methodological issues, setting the stage for the more than 400 GWAS that were to follow. These GWAS have so far identified more than 250 loci at which common variants influence the predisposition to diseases that are common (i.e., diabetes, autoimmune diseases, and several types of cancer), an achievement that by far outweighed that of the previous decade of genetic studies. Results are available in the catalogue of published GWAS prepared by the National Cancer Institute (NCI)-National Human Genome Research Institute (NHGRI). (Hindorff et al., 2010) The genetic variants that can be identified by GWAS are common variants (with at least 5% frequency in the population) and have a low effect size; the conferred relative risks, as expressed by odds ratio, usually range between 1.1 and 1.5. These results confirm the views that the genetic predisposition to common diseases consists of the combined effect of numerous common genetic variants, each of a small effect size. However, it should be noted that GWAS identify regions of the genome (loci) rather than variants of specific genes. Indeed, the specific variant(s) identified by GWAS may simply represent the signal of one or more hidden variant(s) (not typed in the arrays used in GWAS). Limitations of GWAS need to be mentioned. First, these studies need very large samples of cases and controls. Second, DNA and data quality control procedures and statistical analysis need to be carried out by expert centers. Third, the overall cost of GWAS, ranging from hundreds of thousands to millions of US dollars, is prohibitive for most research groups worldwide. And finally, even after and in spite of all quality control procedures, there is still the chance that the results of GWAS include false-positive results, so that an independent replication of these results is still important even after testing thousands of individuals (Pier et al., 2010)

3. Candidate genetic factors

CAD is a complex, multifactorial disorder in which interactions among various genetic and environmental influences play an important role. Many genes are likely to be involved in some way in the process for CAD (Table 1). Some genetic studies have suggested that several gene polymorphisms, including those in the genes for angiotensin-converting enzyme (Samadi et al., 2009) and paraoxonase (Fallah et al., 2010) increase the risk for CAD. Polymorphisms in the genes for insulin-like growth factor-I and lipoprotein lipase have been shown to increase the risk of both CAD and type 2 diabetes (Wang et al., 1996; Vaessen et al., 2001).

There are certain genetic defects that affect activities of some enzymes (cystathionin β-synthase, methyltransferase and 5, 10-methylenetetrahydrofolate reductase) which may lead to homocystinuria. Heterozygosity for deficiency of cystathionin β-synthase is known to be linked with arthrosclerosis and thrombotic disease including CAD (Bakir et al., 2001).

Adiponectin gene locus, chromosome 3q27, is the candidate site for CAD. Adiponectin I164T mutation is associated with the metabolic syndrome and coronary artery disease. The I164T mutation in the adiponectin gene is reported to be a common genetic background associated with the metabolic syndrome and CAD in the Japanese population (Ohashi et al., 2004)

The Von Willebrand factor (VWF) may be causally associated with coronary heart disease or merely be a marker of endothelial damage. The G allele of the -1793 C/G promoter polymorphism in the VWF gene has been associated with higher plasma levels of VWF. Van

der Meer et al., (Van der Meer et al., 2004) found a clear association of G allele of the -1793 C/G polymorphism in the VWF gene with an increased risk of Coronary heart disease.

Location	Gene name/Polymorphisms
17q23	Angiotensin-Converting Enzyme insertion/deletion (intron 16)
1q42-q43	Angiotensinogen Met235Thr, −6G/A
3q21-q25	Angiotensin II type1 Receptor 1166A/C
8q21-q22	Aldosterone Synthase (CYP11B2) −344T/C, Lys173Ar
14q32.1-q32.2	Bradykinin B2 receptor gene −58T/C
6p24.1	Endothelin-1 Lys198Asn
7q36	eNOS Glu298Asp, −786T/C
17q21.32	Glycoprotein IIIa P1A1/A2
5q23-31	Glycoprotein Ia 807T/C
17pter-p12	Glycoprotein Ib*a* Thr145Met
4q28	*β*fibrinogen −455G/A
11p11-q12	Prothrombin 20210G/A
7q21.3-q22	PAI-1 4G/5G (promoter region)
7q21.3	Paraoxonase1 Arg192Gln, Leu54Met
8p12-p11.2	Werner Helicase Gene Cys1367Arg
1p36.3	Methylenetetrahydrofolate reductase 677C/T
16q24	NADH/NADPH oxidase p22phox242C/T, 640A/G
5q31.1 CD14	Monocyte Receptor −260C/T
11q22.3	Stromelysin (MMP3) 5A/6A (promoter region)
20q11.2-q13.1	Gelatinase B (MMP9) −1562C/T
19q13.2	ApolipoproteinE E2/E3/E4
16q21	Cholesteryl Ester Transfer Protein (CETP) Ile405Val
9q31.1	ABCA1 gene Ile823Met
3p25	PPAR-gamma Pro12Ala, Pro115Gln
20q13.11-q13.13	Prostacyclin synthase gene

Table 1. The common genetic polymorphisms which are thought to be associated with myocardial infarction or coronary artery disease.

4. Novel genetic risk factors

4.1 MLXIPL

Triglycerides are produced from either fatty acids obtained directly from the diet or synthesized *de novo* when excess carbohydrates are consumed. Genes that respond to glucose contain a specific regulatory site, the carbohydrate response element (ChoRE), in their promoter regions. To date, ChoREs have been mapped within the promoter regions of the liver-type pyruvate kinase (PK), S14, fatty acid synthase (FAS), acetyl-CoA carboxylase 1 (ACC), and thioredoxin-interacting protein genes (Towle et al., 2005; Minn et al., 2005).
ChREBP is a basic helix-loop helix/leucine zipper transcription factor involved in mediating glucose-responsive gene activation (Yamashita et al., 2001). Mice with a disruption of the

ChREBP gene or hepatocytes treated with siRNA to reduce ChREBP expression cannot induce lipogenic gene expression in response to carbohydrate (Iizuka et al., 2004; Dentin et al., 2004). In hepatocytes prepared from ChREBP null mice, the induction can be restored by the addition of a ChREBP expression vector (Ishii et al., 2004). Thus, ChREBP is essential for regulating lipogenic gene expression. However, it has previously reported that ChREBP requires an interaction partner, Mlx, to efficiently bind to ChoRE sequences and exert its functional activity (Stoeckman et al., 2004). Mlx is a basic helix-loop helix/leucine zipper protein that heterodimerizes with several partners, including ChREBP; MondoA, a paralog of ChREBP expressed predominantly in skeletal muscle; and the repressors Mad1, Mad4, and Mnt (Billin et al., 2000; Billin et al., 1999; Meroni et al., 2000). Expressing a dominant negative form of Mlx in hepatocytes completely inhibits the glucose response of a number of lipogenic enzyme genes, including PK, S14, ACC, and FAS (Ma et al., 2005). This inhibition is rescued by overexpressing ChREBP but not MondoA. Therefore, Mlx is an obligatory partner of ChREBP in regulating glucose-responsive lipogenic enzyme genes.
Recently, SNPs localized within the MLXIPL (MLX intracting protein like; ChREBP, carbohydrate response element binding protein) loci have been associated with plasma triglycerides (Kooner et al., 2008; Kathiresan et al., 2008). The most significant association was described for the rs3812316 SNP (C771G, His241Gln); the CC genotype was associated with elevated TGs. The identified SNP is located at evolutionary conserved domain responsible for glucose dependent activation of MLXIPL. After activation and binding to the MLX, the complex increases the transcription of genes involved, among others, in lipogenesis and triglyceride synthesis. Since, elevated plasma triglycerides (TG) are an independent risk factor for cardiovascular disease development (Sarwar et al., 2007) and MLXIPL loci have been associated with plasma triglycerides, this gene might be a novel genetic risk factor for coronary artery disease (Pan et al., 2009)

4.2 Resistin

Resistin is a 10 kDa protein composed of 94 amino acids. It was cloned in 2001 and was shown to be a thiazolidinedione (TZD)-regulated cytokine expressed in adipose tissue (Wolf et al., 2004). The effect of resistin on insulin action has been extensively investigated in laboratory models. It was shown to be involved in hepatic glucose and lipid metabolism and appears to play a pivotal role in hepatic insulin resistance (IR) induced by high-fat diet (Rajala et al., 2003). Resistin was suggested to affect endothelial function and the migration of vascular smooth muscle cells (Cohen & Horel., 2009), which are regarded as key pathophysiological mechanisms of atherosclerosis. Further, resistin has been noted to play a vital role in increasing the level of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in an obese person (Rizkalla et al., 2009) which is directly atherogenic. Resistin induces increases in MCP-1 and sVCAM-1 expression in vascular endothelial cells which suggest a possible mechanism that contribute to atherogenesis (Cohen & Horel., 2009). Recent reports indicate that resistin promotes proliferation of VSMC that occurs through both ERK 1/2 and Akt signalling pathways (Calabro et al., 2004). Thus resistin is noted to enhance VSMC migration, which is a known component of athermanous plaque synthesis (Verma et al., 2003). Resistin promotes foam cell formation via dysregulation of scavenger receptors (SR-A) and ATP-binding cassette transporter-A1 (ABCA1) (Lee et al., 2009) through PPAR gamma. In atherosclerosis, increased level of resistin causes elevation of soluble TNF-_ receptor 2, IL-6 and lipoprotein-associated phospholipase A2 (Lp- PLA2) (Reilly et al., 2005).

With respect to the reported resistin variants, the mostly extensively studied has been the promoter variant SNP-420C>G. Functional binding studies have been done with stimulatory proteins (Sp)-1 and 3, which bind to the promoter. Their binding has been described to be influenced by SNP-420C>G. Sp-1 and 3 were discovered to bind efficiently only to the G-allele sequence and after binding to increase the activity of the promoter. (Chung et al., 2005). It seems likely that the more active promoter with the SNP-420C>G G allele is the reason for several observations of higher plasma resistin concentration in the G allele carriers (Yamauchi et al., 2008). However, in contrast to these studies, it has also been reported that the genotypes of SNP-420C>G do not influence the plasma resistin concentration in Italian subjects (Norata et al., 2007). Furthermore in a small study of polycystic ovary syndrome patients noassociation was detected between SNP-420C>G genotype and the serum level of resistin (Escobar-Morreale et al., 2006).
Recent studies have shown that the resistin levels are significantly correlated with coronary artery calcification and are predictive of coronary atherosclerosis in humans (Mohty et al., 2009). Previous studies described the association among this -420 (C>G) polymorphism, the resistin levels and cardiovascular risk factors (Ukkola et al., 2006; Norata et al., 2007**)** However, the association between the serum resistin levels and CHD seemed to be negative, and might be controversial for this polymorphism and CAD. (Norata et al., 2007; *Kunnari et al*. 2005) Differences in the cohorts might explain the different results, depending on which ethnic group was tested (Menzaghi et al., 2006; Hivert et al., 2009). Indeed, methodological limitations in the commercially available ELISA assays might also result in variations among serum levels, which might cause difficulties when comparing results from different publications.

4.3 Renalase

The kidney, in addition to maintaining fluid and electrolyte homeostasis, performs essential endocrine functions (Peart et al., 1977). Patients with end-stage renal disease are at high risk for cardiovascular events, even when provided optimal renal replacement therapy (Go et al., 2004; Anavekar et al., 2004). It has been suggested that failure to replicate the endocrine functions of the kidney may contribute to this risk, in association with heightened sympathetic tone (Joles & Koomans 2004; Neumann et al., 2004; Wolfe et al., 1999). Renalase, a flavin adenine dinucleotide-dependent amine oxidase that is secreted into the blood by the kidney, metabolizes circulating catecholamines, and is deficient in chronic kidney disease (Xu et al., 2005). Excess catecholamines promote the activity, secretion, and synthesis of renalase, providing a novel pathway of negative feedback homeostatic control (Li et al., 2008). In rodents, parenteral administration of renalase lowers blood pressure, heart rate, and cardiac contractility (Xu J, Desir GV 2007). During cardiac ischemia in rats, infusion of recombinant renalase reduces myocardial infarct size whereas neonatal nephrectomy leads to elevated sympathetic nervous system activity, renalase deficiency, and cardiac hypertrophy (Desir 2008; Ghosh et al., 2008). Human renalase is encoded by a 311Kbp gene with 10 exons located on chromosome 10q23.33. The major isoform of renalase contains 342 amino acids comprising a signal peptide (amino acids 1–17), a flavin-adenine dinucleotide (FAD) binding domain (amino acids 4–45), and a monoamine oxidase domain (amino acids 75–342). Evidence exists for at least four alternatively- spliced isoforms of renalase (Desir, 2009). The most common isoform (renalase1) is encoded by exons 1–4, 6–7, and 9. It is the predominant human renalase protein detectable in plasma, kidney, heart, skeletal muscle,

and liver. The functional significance of the spliced isoforms is not known. It has weak AA similarities to MAO-A and MAO-B and distinct substrate specificity and inhibitor profile, which indicates that it represents a new class of FAD-containing monoamine oxidases. MAO-A and MAO-B are FAD containing, mitochondrial enzymes that metabolize intracellular catecholamines. MAO-A and MAO-B have overlapping substrate specificity; catabolize neurotransmitters such as epinephrine, norepinephrine, serotonin, and dopamine; and are specifically inhibited by clorgyline and deprenyl, respectively. Polyamine oxidase, the other known FAD-containing oxidase, is an intracellular oxidase that metabolizes spermine and spermidine and regulates cell growth (Jalkanen & Salmi, 2001). Unlike MAO-A and MAO-B, which are anchored through the carboxyl terminus to the outer mitochondrial membrane (Binda et al., 2002) and confined to intracellular compartments, renalase is secreted into the blood, where it is detectable by Western blotting. Amine oxidase activity has been measured in human plasma and is believed to be mediated by vascular adhesion protein 1 (VAP-1), a copper-containing semicarbazide-sensitive amine oxidase that is secreted by smooth muscle cells, adipocytes, and endothelial cells (Salmi & Jalkanen, 2001). VAP-1's substrate specificity and inhibitor profile are very different from that of renalase. It metabolizes benzylamine and methylamine and is inhibited by semicarbazide and hydroxylamine. Therefore, renalase is the only known amine oxidase that is secreted into blood and that metabolizes circulating catecholamines. While the hypotensive effect of renalase can be fully accounted for by the observed decrease in contractility and heart rate, we cannot categorically exclude the possibility that renalase's effect may be partly receptor mediated.

A common missense polymorphism in the flavin-adenine dinucleotide-binding domain of human renalase (Glu37Asp) has recently been described. This is the only reported common coding single-nucleotide polymorphism in the renalase gene, and was recently found to be associated with essential hypertension (Zhao et al., 2007). Whether common genetic variation at this locus affects cardiac structure, function, and ischemia in humans is not known.

4.4 P-selectin

P-selectin (GMP-140; granule membrane protein-140) is an adhesion molecule which mediates the interaction of activated endothelial cells or platelets with leukocytes. The selectin family of adhesion molecules also comprises E- and L-selectin. The genes coding for the three selectins are clustered on chromosome 1q21–q24 (Watson et al., 1990). The P-selectin gene spans >50 kb and contains 17 exons, most of which encode structurally distinct domains. P-selectin is stored in a-granules of platelets and the Weibel–Palade bodies of vascular endothelial cells (McEver et al., 1989) it rapidly shifts from the membranes of secretory granules to the surface of platelets and endothelial cells upon stimulation by oxidized low density lipoprotein (LDL) (Vora et al., 1997), oxygen radicals (Patel et al., 1991), thrombin (Lorant et al., 1991), cytokines and various other stimuli (Zimmermann, et al., 1990). P-selectin is required for efficient recruitment of neutrophils in acute and chronic inflammation (Johnson, R.C., et al. 1995) and recently has been shown to bind T cells on vascular endothelial cells. These properties suggest that P-selectin could contribute to atherogenesis (Hansson, G.K. , 1989, Libby, P. and Hansson, G.K.,1991). Actually, P-selectin expression has been demonstrated to be significantly increased in endothelium overlying atherosclerotic plaques, and it is focally expressed in the aorta of hypercholesterolemic

rabbits. It has been reported that P-selectin-deficient mice on an atherogenic diet develop significantly smaller fatty streaks than non-deficient mice (Johnson, R.C., et al. 1997). In humans, plasma P selectin levels have been shown to be increased in diabetic patients, in patients with unstable angina, post-angioplasty restenosis and after coronary artery spasm (Kaikita, K. , 1995).

Recent study that genotyped 5 single nucleotide polymorphisms (SNPs) in P-selectin (*SELP*) (V168M, S290N, N592D, V599L, T715P), 2 SNPs (M62I, S273F) in P-selectin glycoprotein ligand-1 (*SELPLG*), 5 SNPs in *CD40LG* (−3459A>G, −122A>C, −123A>C, 148T>C, intr4–13T>C), the H558R SNP in *SCN5A*, and rs2106261 in *ZFHX3*. In addition, length polymorphisms in *SELPLG* (36bp-tandem repeat) and *CD40LG* (CA-repeat) were genotyped by PCR methods. None of the gene polymorphisms showed significant differences between AMI patients and healthy controls. Among patients with a history of VF (Ventricular fibrillation), however, the SELP 168M variant showed a significantly higher prevalence as compared with patients without VF. This was the first description of an association of the SELP gene variant 168M with primary VF during acute MI. This variant may be a novel polymorphism for evaluating the susceptibility for VF in the setting of acute MI. (Elmas, 2010)

4.5 KDR

Kinase insert domain-containing receptor/fetal liver kinase-1, also called VEGFR2 (KDR), is expressed in a wide variety of cells such as endothelial progenitor cells (EPCs), endothelial cells, and primitive and more mature hematopoietic cells. Kinase insert domain-containing receptor/ fetal liver kinase-1 is required for the differentiation of EPCs and for the movement of EPCs from the posterior primitive streak to the yolk sac, a precondition for the subsequent formation of blood vessels (Shalaby et al., 1997). Studies with *KDR* knockout mice have found that KDR plays critical roles in the development and formation of blood vessel networks (Fong et al., 1995). Vascular endothelial growth factor binds to 2 tyrosine kinase receptors, VEGF receptor-1 (VEGFR1, Flt-1) and KDR, in endothelial cells. The mitogenic and chemotactic effects of VEGF are mediated mainly through KDR in endothelial cells VEGF receptor signal transduction which is activated through autophosphorylation of tyrosine residues in the cytoplasmic kinase domain of KDR. This event is followed by activation of downstream signaling pathways such as mitogen-activated protein kinases, Akt and eNOS, which are essential for migration and proliferation of endothelial cells, thereby stimulating angiogenesis (Matsumoto & Claesson-Welsh, 2001). After vascular endothelial growth factor (VEGF) binding to KDR, multiple early signaling cascades are activated in EPCs and in endothelial cells. An array of biological activities are subsequently elicited in vivo and in vitro, including angiogenesis, endothelial survival, proliferation, migration, and increased production of nitric oxide and prostaglandin I2 (Gerber et al., 1994). Dysregulated vessel growth is implicated in the pathogenesis of a wide variety of diseases, including proliferative retinopathies, tumors, rheumatoid arthritis, atherosclerosis, as well as CHD. (Dimmeler et al., 2001; Rehman et al., 2004; Werner et al., 2002). The variation of *KDR* gene may change the biological function of KDR. Bioinformatic analysis showed that the single nucleotide polymorphism (SNP) -604T/C (rs2071559) leads to structural alteration of the binding site for transcriptional factor E2F (involving in cell cycle regulation, interacting with Rb p107 protein) in *KDR* gene promoter region, which may alter KDR expression. Exonic polymorphisms SNP1192G/A (rs2305948, in exon 7) and SNP1719A/T (rs1870377, in exon 11) are located in the third and fifth NH2-terminal IG-like

domains within the extracellular region, which are important for ligand binding, and result in nonsynonymous amino acid changes at residue 297V/I and 472H/Q, respectively. It is showed that patients carrying the KDR mutations are more susceptible to CHD. The higher CHD risk could be due to downregulation of the VEGF/KDR signaling pathway. However, the angiogenesis preceded by VEGF/KDR signaling pathway could be decreased due to low KDR activity. The SNP-604T/C decreases mRNA levels of KDR and both SNP1192G/A and SNP1719T/A resulted in slight but significant decrease in the VEGF binding efficiency to KDR. One can speculate that the decrease in KDR function is correlated with vascular dysfunction, including endothelial cell damage, impaired endothelial cell survival, decreased antiapoptotic effects of VEGF, and abnormal vascular repair. All of these can promote the progression of atherosclerotic disease. A previous study has suggested that -907T/C, -11903G/A, and -18487A/T (now called SNP-604, SNP1192, and SNP1719, respectively) have no significant association with the development of coronary artery lesion in Japanese subjects with Kawasaki disease (Kariyazono et al., 2004). The differences between the studies could be due to the different pathologic mechanism between the coronary artery lesion with Kawasaki disease and CHD, different genetic background of the populations as well as the sample size in different studies. (Schmidt-Lucke et al., 2005). The genotype frequencies of the 3 SNPs from the HapMap data were similar to others. The rs2071559 can capture rs7667298 (exon_1, untranslated). No linkage disequilibrium was found in rs2305948 with other SNPs in HapMap CHB data. The rs1870377 (exon_11) can capture rs10016064 (intron_13), rs17085265 (intron_21), rs3816584 (intron_16), rs6838752 (intron_17), rs1870379 (intron_15), rs2219471 (intron_20), rs1870378 (intron_15), rs13136007 (intron_13), and rs17085262 (intron_21). The results showed that 2 blocks were captured by SNP-604 (rs2071559) and SNP1719 (rs1870377), respectively, and SNP1192 (rs2305948) were associated with CHD.

5. Other novel polymorphisms

Asymmetrical dimethylarginine (ADMA), an endogenous arginine analogue, inhibits nitric oxide synthases and plays an important role in endothelial dysfunction. The results suggest that the DDAH1 (dimethylarginine dimethylaminohydrolase 1) loss-of-function polymorphism is associated with both increased risk of thrombosis stroke and CAD (Ding et al., 2010). Growing evidence has shown that inflammation plays crucial roles in the development of coronary artery disease. Interleukin-16 (IL-16), a multifunctional cytokine, is involved in a series of inflammatory disorders. One finding indicates that *IL-16* may be used as a genetic marker for CAD susceptibility (Wu et al., 2010). Two single-nucleotide polymorphisms (SNPs), rs1746048 and rs501120, from genome wide association studies of coronary artery disease map to chromosome 10q11 ~80 kb downstream of chemokine *CXCL12*. Coronary artery disease risk alleles downstream of *CXCL12* are associated with plasma protein levels of CXCL12 and appear to be related to *CXCL12* transcript levels in two human cell lines. This implicates *CXCL12* as potentially causal and supports CXCL12 as a potential therapeutic target for CAD (Nehal et al., 2011).

6. Conclusion

Studying only one SNP may be an overly simplistic method in investigating a complex disease such as CAD. Complex traits such as CAD, more large databases of high-quality

genetic and clinical data need to be established and since genes and environmental factors are both involved in this disease; environmental causes and gene-environment interactions must be carefully assessed. These results will provide clues to the involvement and investigation of novel candidate genes in association studies. Large replication studies with different ethic samples are needed to investigate whether there are ethnic differences in the influence of novel polymorphisms on coronary artery disease. This issue should be investigated with different ethnic samples in the future. Therefore studies with large sample size of coronary artery disease and different ethnicity will be welcome to help elucidate the interconnection between novel genetics and pathogenesis of coronary artery disease.

7. Abbreviations

ABCA1: ATP-binding cassette transporter 1
ACC: acetyl-CoA carboxylase
ALOX5AP: Arachidonate 5-lipoxygenase-activating protein.
APOA1: Apolipoprotein A1
CAD: Coronary artery disease
LCAT: Lecithin-cholesterol acyltransferase
CHD: Coronary heart disease
ChoRE: Carbohydrate response element
ChREBP: Carbohydrate response element binding protein
ELISA: Enzyme-linked immunosorbent assay
EPCs: Endothelial progenitor cells
ERK 1/2 : Extracellular signal-regulated kinases1/2
FAD: Flavin-adenine dinucleotide
FAS: Fatty acid synthase
GWAS: Genome-wide association Studies
HDL: High-density lipoprotein
KDR: Kinase insert domain-containing receptor
Lp- PLA2: Lipoprotein-associated phospholipase A2
Mad1: Mitotic arrest deficient-like 1
Mad4: Mitotic arrest deficient-like 4
MAO-A: L-Monoamine oxidases A
MAO-B : L-Monoamine oxidases B
MEF2A: Myocyte enhancer factor 2A
MlX: Max-like x protein
PPAR: Peroxisome proliferator-activated receptors
PK : Pyruvate kinase
siRNA: Small interfering RNA
SNPs: Single nucleotide polymorphisms
Sp1: stimulatory proteins 1
SR-A: Scavenger receptors A
TNF: Tumor necrosis factors
VAP-1: vascular adhesion protein 1
VCAM-1: Vascular cell adhesion protein 1
VF: Ventricular fibrillation
VLDL: Very low density lipoprotein
VWF: Von Willebrand factor

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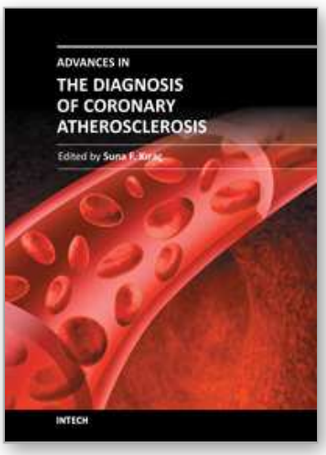

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Coronary artery disease (CAD) and its consequences are most important morbidity and mortality reasons in the developed and developing countries. To prevent hard end-points, early definitive diagnosis and optimum therapy play significant role. Novel advanced diagnostic tests which are biomarkers of inflammation, cell adhesion, cell activation and imaging techniques provide to get the best result in the detection and characterization of calcified or uncalcified atherosclerotic plaques. In spite of last developments in the imaging methods, coronary catheterization is still frequently performed. Following the first cardiac catheterization performed in 1844, date by date historical developments and the mechanics of cardiac catheterization techniques, risks associated with coronary angiography, and also, preventions and treatments of possible complications have been presented in this book. Other important issue is radiation exposure of patients and staff during coronary angiography and scintigraphy. Radiation dose reduction techniques, general radiation protection principles have been discussed in related chapters.

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