UNIVERSITI PUTRA MALAYSIA

IDENTIFICATION OF CANDIDATE GENES EXPRESSIONS AND POLYMORPHISMS ASSOCIATED WITH ATHEROSCLEROSIS FROM POSTMORTEM CASES IN HOSPITAL KUALA LUMPUR AND HOSPITAL SERDANG, MALAYSIA

JOAN ANAK BLIN

FPSK(M) 2013 52

IDENTIFICATION OF CANDIDATE GENES EXPRESSIONS AND POLYMORPHISMS ASSOCIATED WITH ATHEROSCLEROSIS FROM POSTMORTEM CASES IN HOSPITAL KUALA LUMPUR AND HOSPITAL SERDANG, MALAYSIA

JOAN ANAK BLIN

MASTER OF SCIENCE
UNIVERSITI PUTRA MALAYSIA

2013

IDENTIFICATION OF CANDIDATE GENES EXPRESSIONS AND POLYMORPHISMS ASSOCIATED WITH ATHEROSCLEROSIS FROM POSTMORTEM CASES IN HOSPITAL KUALA LUMPUR AND HOSPITAL SERDANG, MALAYSIA

By

JOAN ANAK BLIN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

September, 2013

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

IDENTIFICATION OF CANDIDATE GENES EXPRESSIONS AND POLYMORPHISMS ASSOCIATED WITH ATHEROSCLEROSIS FROM POSTMORTEM CASES IN HOSPITAL KUALA LUMPUR AND HOSPITAL SERDANG, MALAYSIA

By

JOAN ANAK BLIN

September 2013

Chairperson: Zalinah bte Ahmad, PhD

Faculty: Medicine and Health Sciences

Atherosclerosis as presented by coronary artery disease is a slow progressing, pathological process of plaque formations within arteries. Differential expression of susceptibility genes plays important role in the pathogenesis of atherosclerosis. This study aimed to determine differential expression of 11 candidate genes and polymorphisms associated with atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang. Seventy six atherosclerotic coronary artery tissues (ACAT) (cases) and 149 non-atherosclerotic coronary artery tissues (NCAT) (healthy controls) were gathered from the Forensic Department of Hospital Kuala Lumpur and Hospital Serdang based on predetermined inclusion and exclusion criteria. Gross examination findings showed the presence of mild to severe atheroma in ACAT samples, whereas NCAT samples showed clean tissues. Microscopic findings of ACAT samples showed presence of both stable (80.3%) and unstable atheroma (19.7%) respectively, with 11.8% of the samples were superimposed with thrombosis. Six RNA samples of each ACAT and NCAT were analyzed using

GenomeLab Genetic Analysis System (GeXP). Student's *t*-test showed significant increase in expression levels of low density lipoprotein receptor (*LDLR*), tumor protein 53 (*TP53*), and matrix metalloproteinase 9 (*MMP9*) genes in ACAT samples ($p< 0.05$). No significant differences in the expression levels were obtained for the remaining eight candidate genes. Restriction fragment length polymorphism (RFLP) analysis was performed on 76 ACAT and 149 NCAT samples to investigate the variation in *LDLR* (C88S), *TP53* (*TP53* codon 72), and *MMP9* (*MMP9*-1562C>T) genotypes. Descriptive statistics were used to determine genotypes distribution of each polymorphism in both groups. The Chi-square (χ^2) test revealed significant differences in CT genotype and T allele of *MMP9*-1562C>T polymorphism when compared between the ACAT and NCAT groups (CT: χ^2= 19.758, *df*= 1, *p*= 0.000 and T allele: χ^2= 21.109, *df*= 1, *p*=0.000). The CT genotype and the T allele were significantly higher in ACAT samples (CT: 57.9% in ACAT vs. 27.5% in NCAT and T allele: 77.9% in ACAT vs. 48.3% in NCAT). There were positive associations of CT genotype and T allele with atherosclerosis (CT: OR= 3.622, 95% CI= 2.028 – 6.470 and T allele: OR= 3.780, 95% CI= 0.2115 – 6.755). There were no significant differences of CT genotype and T allele distribution among the three major ethnicities and between genders of the healthy population. No significant associations were identified in the C88S and *TP53* codon 72 polymorphisms with regard to atherosclerosis risk. In conclusion, CT genotype and T allele of the *MMP9*-1562C>T polymorphism displayed associations with the risk of developing atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENGENALPASTIAN EKSPRESI CALON GEN DAN POLIMORFISME BERKAITAN DENGAN ATEROSKLEROSIS DARIPADA KES-KES BEDAH SIASAT DI HOSPITAL KUALA LUMPUR DAN HOSPITAL SERDANG, MALAYSIA

Oleh

JOAN ANAK BLIN

September 2013

Pengerusi: Zalinah bte Ahmad, PhD

Fakulti: Perubatan dan Sains Kesihatan

Aterosklerosis yang ditunjukkan melalui penyakit arteri koronari adalah proses patologi pembentukan plak secara perlahan di dalam arteri. Pengekspresan berbeza oleh gen-gen berkaitan memainkan peranan penting dalam patogenesis aterosklerosis. Kajian ini bertujuan untuk menentukan ekpresi 11 calon gen dan polimorfisme-polimorfisme yang berkaitan dengan risiko aterosklerosis daripada kes-kes bedah siasat di Hospital Kuala Lumpur dan Hospital Serdang. Tujuh puluh enam tisu arteri koronari aterosklerotik (ACAT) (kes) dan 149 tisu arteri koronari bukan aterosklerotik (NCAT) (kawalan sihat) telah dikumpul dari Jabatan Forensik Hospital Kuala Lumpur dan Hospital Serdang berdasarkan kriteria-kriteria penglibatan dan pengecualian yang telah ditetapkan. Penemuan pemeriksaan “mata kasar” menunjukkan kehadiran ateroma daripada sederhana kepada teruk dalam sampel ACAT, sementara sampel NCAT menunjukkan tisu-tisu bersih. Penemuan mikroskopik terhadap sampel ACAT menunjukkan kehadiran kedua-dua ateroma stabil (80%) dan tidak stabil (19.7%), dengan 11.8% daripada sampel tersebut

menunjukkan thrombosis yang bertindih. Enam sampel RNA daripada setiap ACAT dan NCAT telah dianalisis menggunakan Sistem Analisis Genetik GenomeLab (GeXP). Ujian-t menunjukkan peningkatan yang signifikan dalam tahap ekpresi gen-gen reseptor lipoprotein ketumpatan rendah (*LDLR*), protein tumor 53 (*TP53*), dan metalloproteinase matriks 9 (*MMP9*) di dalam sampel ACAT ($p< 0.05$). Tiada perbezaan yang signifikan dalam tahap ekspresi yang telah diperoleh untuk kelapan-lapan baki gen lain. Analisis polimorfisme panjang serpihan penyekatan (RFLP) telah dilakukan ke atas 76 sampel ACAT dan 149 sampel NCAT untuk menyiasat variasi dalam genotip-genotip *LDLR* (C88S), *TP53* (*TP53* codon 72), dan *MMP9* (*MMP9*-1562C>T). Statistik deskriptif telah digunakan untuk menentukan taburan genotip setiap polimorfisme di dalam kedua-dua kumpulan. Ujian Chi-square (χ^2) telah menunjukkan perbezaan yang signifikan terhadap genotip CT dan alel T dalam polimorfisme *MMP9*-1562C>T semasa perbandingan di antara kumpulan ACAT dan NCAT (CT: χ^2= 19.758, *df*= 1, *p*= 0.000 dan alel T: χ^2= 21.109, *df*= 1, *p*=0.000). Genotip CT dan alel T secara signifikan lebih tinggi di dalam sampel ACAT (CT: 57.9% di dalam ACAT vs. 27.5% di dalam NCAT dan alel T: 77.9% di dalam ACAT vs. 48.3% di dalam NCAT). Terdapat perkaitan yang positif bagi genotip CT dan alel T dengan aterosklerosis (CT: OR= 3.622, 95% CI= 2.028 – 6.470 dan alel T: OR= 3.780, 95% CI= 0.2115 – 6.755). Walau bagaimanapun, tidak terdapat perbezaan yang ketara pada taburan genotip CT dan alel T di kalangan tiga etnik utama dan antara jantina populasi yang sihat. Tiada perkaitan yang signifikan dikenalpasti di dalam polimorfisme C88S dan *TP53* codon 72 ke atas risiko aterosklerosis. Kesimpulannya, genotip CT dan alel T bagi polimorfisme *MMP9*-1562C>T telah menunjukkan perkaitan dengan risiko mendapat aterosklerosis daripada kes-kes bedah siasat di Hospital Kuala Lumpur dan Hospital Serdang.

ACKNOWLEDGEMENT

Firstly, I would like to dedicate my deepest thanks to God for blessing me with the patience to complete this study with success.

I would like to express my deepest gratitude to my supervisor, Dr. Zalinah bte Ahmad, for her valuable ideas, advice, guidance and support throughout this whole project. Without her help and support, this project is difficult to be completed.

I would also like to sincerely thank my co-supervisor, Prof. Dr. Lekhraj Rampal S/O Gyanchand Rampal, for his idea, help and advice.

Sincere appreciation is also extended to all staffs of the Chemical Pathology Laboratory and Histopathology Laboratory, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM), Molecular Genetic Laboratory of Institute of Bioscience, UPM, and Forensic Department of Hospital Serdang, Selangor and Hospital Kuala Lumpur, Malaysia. Their immeasurable supports, assistances and helps are truly appreciated.

My deepest gratitude also goes to my family and group research for their moral supports and encouragement throughout my study.

Last but not least, sincere thanks to grant IRPA 06-02-04-0482 for funding this project.

I certify that a Thesis Examination Committee has met on 27th September 2013 to conduct the final examination of Joan Anak Blin on his thesis entitled " Identification of Candidate Genes Expressions and Polymorphisms Associated with Atherosclerosis from Postmortem Cases in Hospital Kuala Lumpur and Hospital Serdang, Malaysia " in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Sabrina Bte Sukardi, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Huzwah Bte Khaza'ai, PhD
Senior lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Lai Mei I, PhD
Senior lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Shahrul Hisham Bin Zainal Ariffin, PhD
Associate Professor
School of Biosciences and Biotechnology
Faculty of Science and Technology
Universiti Kebangsaan Malaysia
(External Examiner)

NORITAH OMAR, PhD
Associate Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 20 November 2013

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Zalinah bte Ahmad, PhD
Senior lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairperson)

Lekhraj Rampal A/L Gyanchand Rampal, MBBS
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

JOAN ANAK BLIN

Date: 27th September 2013

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

%	Percentage
°C	Degree of Celsius
α	Alpha
β	Beta
μ	Micro
μg	Microgram
μl	Microliter
μm	Micrometre
μM	Micromolar
χ^2	Chi-square test
ABCA1	ATP-binding cassette, subfamily A, member 1
ACAT	Atherosclerotic coronary artery tissue
ALOX5AP	Arachidonate 5-lipoxygenase-activating protein
ANGPTL3	Angiopoietin-like 3
Apo A-I	Apolipoprotein A-I
APOA3	Apolipoprotein A3
APOA4	Apolipoprotein A4
APOA5	Apolipoprotein A5
APOB	Apolipoprotein B
APOB100	Apolipoprotein B-100
APOC	Apolipoprotein C
ApoE	Apolipoprotein E
ApoE ε2	Apolipoprotein E ε2 allele
ApoE ε3	Apolipoprotein E ε3 allele
ApoE ε4	Apolipoprotein E ε4 allele
ASP-PCR	Allele-specific primer polymerase chain reaction
ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O

	subunit
AUC	Area-under-the-curve
bp	Base pairs
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBS	Cystathionine-beta-synthase
cDNA	Complementary Deoxyribonucleic acid
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
df	Degree of freedom
DNA	Deoxyribonucleic acid
DNase	Anti-Deoxyribonuclease
EST	expression sequence tag
FH	Familial hypercholesterolemia
g	Centrifugation force
GALNT2	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2
GCKR	Glucokinase regulatory protein
GeXP	GenomeLab Gene Expression Profiler
H & E	Haematoxylin and eosin staining
HDL	High density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
IHD	Ischemic heart disease
IRS1	Insulin receptor substrate 1
Knar	Kanamycin gene
LAD	Left anterior descending

LCAT	Lecithin-cholesterol acyltransferase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
LIPG	Endothelial lipase gene
LMNA	Lamin A/C gene
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
MALDI-TOF-MS	Matrix-assisted laser desorption ionization time-of-light mass spectrometry
MCP-1	Monocyte chemoattractant protein-1
mg	Milligram
$MgCl_2$	Magnesium chloride
MLXIPL	MLX interacting protein-like
mM	Millimolar
MMAB	Methylmalonic aciduria (cobalamin deficiency) cblB type
MMP9	Matrix metalloproteinase 9
MMPs	Matrix metalloproteinases
mRNA	messenger Ribonucleic acid
MTHFR	5,10-methylenetetrahydrofolate reductase
MVK	Mevalonate kinase
n	Sample size
NADPH	Nicotinamide adenine dinucleotide phosphate
NCAN	Chondroitin sulfate proteoglycan 3 (neurocan)
NCAT	Non-atherosclerotic coronary artery tissue
ng	Nanogram
NO	Nitric oxide
OR	Odds ratio
p	Significant alpha value

p_1	Estimate exposure rate (proportion exposed) in cases
PCSK9	Proprotein convertase subtilisin/kexin type 9
p_o	Estimated exposure rate (proportion exposed) in controls
R	Relative risk
RFLPs	Restriction Fragment Length Polymorphisms
RIN	RNA integrity number
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RPLP0	Ribosomal protein, large, P0
RT	Reverse transcription
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAGE	Serial analysis of gene expression
SD	Standard deviation
SMCs	Smooth muscle cells
SNPs	Single nucleotide polymorphisms
SORT1	Sortilin 1
SPSS	Statistical Package for Social Sciences
TAFI	Thrombin-activatable fibrinolysis inhibitor
TBE	Tris-Borate-EDTA
TCEP	Tris (2-carboxyethyl) phosphine
TCFA	Thin cap fibroatheroma
TGFBR2	Transforming growth factor, beta receptor II
THBD	Thrombomodulin
TP53	Tumor protein p53
TRIB1	Tribbles homolog 1 (Drosophila)
VCAM-1	Vascular cell adhesion protein 1
VLDL	Very low density lipoprotein

CHAPTER 1

INTRODUCTION

1.0 Background of study

Cardiovascular disease (CVD) is a leading cause of death in Malaysia for the last 45 years and remains as a major public health problem globally (Rampal *et al*., 2008). Cardiac related mortality statistics have shown increasing trends in many developing countries, including India, China, Korea and other Asian countries (Cheng *et al*., 2005). Although a lot of effort has been invested for interventions, prevention, and treatments of the disease, cardiac related mortality remains high. Unsurprisingly, this CVD burden in most Asian populations is expected to double over the next decade (Tai *et al*., 2009).

Atherosclerosis as presented by coronary artery disease (CAD) is one of the major contributors of CVD. Atherosclerosis is a slow progressing, pathological process of plaque formations within the intima of coronary arteries. It develops asymptomatically for decades, and usually is advanced by the time symptoms occur. This phenomenon poses a big challenge for treatments of atherosclerotic vascular disease (Graham and O'Callaghan, 2003).

One of the strategies for better management of the disease is through personalized medicine approach. Personalized medicine is particularly based on the science of pharmacogenomics, a study on how individual's genetic inheritance affects the body's response to drugs. Pharmacogenomics is a combination of traditional pharmacoceutical sciences with knowledge of genes, proteins, and single nucleotide polymorphisms. It is more precise and predictable and may lead us to more accurate diagnoses, safer drug prescribing, and more effective treatment. Personalized medicine approach depends mainly on a comprehensive understanding of the genes and gene variants that contribute to disease susceptibility and progression (Seo *et al*., 2004). Thus, a better understanding on the molecular mechanisms of atherosclerosis is crucial as a fundamental initial step in this long journey.

Candidate gene association study is the most widely used to identify susceptibility genes for coronary artery disease. The approach seeks for associations between phenotype and genotype of the candidate genes (Franchini *et al*., 2008). It is a branch of genome-wide association studies, which has been attempted to assess the role of genes that are already implicated in the pathophysiology of the disease (Lee *et al*., 2009). Candidate genes are predetermined genes located within regions of interest and are identified based on prior knowledge of their function. These candidate genes are suspected of being involved in the expression of a trait that contributes to the disease development. In atherosclerosis, up- or down-regulation pattern of candidate genes have been thought to alter the microenvironment that may protect or worsen the lesion progression (Fortunato and Taranto, 2007). Besides, polymorphisms within susceptibility genes in lipid metabolism, inflammation, and thrombogenesis

are all responsible for atherosclerotic vascular disease susceptibility (Chen *et al*., 2007).

Association studies are designed to compare statistical difference in genotype frequencies between case and control groups, which may offer evidence that a genotype is associated with the trait (Arnett, 2007). A problem with many published association studies is that a positive association observed in one report is often not reproducible in subsequent studies. This scenario is due to inconsistently defined phenotypes, variability in sample size, as well as different populations and ethnic groups under study. Indeed, in single nucleotide polymorphisms (SNPs) analysis, allele frequencies may differ widely in different populations (Gibbons *et al*., 2004). Thus, data collection of genetic variation associated with the risk of developing atherosclerosis in Malaysian population which is also multiracial is very important. This baseline data could lead towards early detection of CVD risk in Malaysia.

Research concerning CAD in Malaysian population is still limited, although its molecular basis has been widely studied in the western world (Abdullah *et al*., 2012). Without proper prevention and managements of CVD, the increasing burden of CVD will directly affect the economic status of the country. More extensive effort is required in molecular aspects so that thorough understanding of the disease is acquired. Therefore, there is an urgent need for a comprehensive study concerning the genetics basis of atherosclerotic vascular disease in Malaysia. The outcome of these fundamental efforts is hoped to facilitate the development of early detection

technique which in turn may contribute to a better prevention action of CVD in Malaysia.

1.1 Research Objectives

General Objective:

1. To study the association between the differential expression of candidate genes and polymorphisms with the risk of developing atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang, Malaysia.

Specific Objectives:

1. To determine the morphology of atherosclerotic coronary artery tissue using haematoxylin and eosin (H & E) staining.
2. To determine list of candidate genes associated with risk of developing atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang, Malaysia using GenomeLab Gene Expression Profiler (GeXP) genetic analysis system.
3. To determine the polymorphisms and distribution of genotypes and alleles frequency of candidate genes associated with risk of developing atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang, Malaysia.

1.2 Hypothesis

There are associations of differential expressions and polymorphisms of candidate genes with the risk of developing atherosclerosis from postmortem cases in Hospital Kuala Lumpur and Hospital Serdang, Malaysia.

REFERENCES

Abdullah, M. H. N., Othman, Z., Noor, H. M., Arshad, S. S., Yusof, A. K. M., Jamal, R. and Rahman, A. R. A. 2012. Peripheral blood gene expression profile of atherosclerotic coronary artery disease in patients of different ethnicity in Malaysia. *Journal of Cardiology* 60: 192-203.

Abilleira, S., Bevan, S. and Markus, H. S. 2006. The role of genetic variants of matrix metalloproteinases in coronary and carotid atherosclerosis. *Journal of Medical Genetics* 43: 897-901.

Adamopoulos, D., Van de Borne, P. and Argacha, J .F. 2008. New insights into the sympathetic, endothelial and coronary effects of nicotine**.** *Clinical and Experimental Pharmacology and Physiology* 35(4): 458-463.

Agarwal, M., Mehta, P. K., Dwyer, J. H., Dwyer, K. M., Shircore, A. M., Nordstrom, C. K., Sun, P., Paul-Labrador, M., Yang, Y. and Merz, C. N. B. 2012. Differing relations to early atherosclerosis between Vitamin C from supplements vs. food in the Los Angeles atherosclerosis study: A prospective cohort study. *The Open Cardiovascular Medicine Journal* 6: 113-121.

Agorastos, T., Masouridou, S., Lambropoulos, A. F., Chrisafi, S., Miliaras, D., Pantazis, K., Constantinides, T.C., Kotsis, A. and Bontis, I. 2004. P53 codon 72 polymorphism and correlation with ovarian and endometrial cancer in Greek women. *European Journal of Cancer Prevention* 13: 277-280.

Aguirre, R. and May, J. M. 2008. Inflammation in the vascular bed: Importance of vitamin C. *Pharmacology & Therapeutics* 119: 96-103.

Akhurst, R. J. 2004. TGFβ signalling in health and disease. *Nature Genetics* 36(8): 790-791.

Akopian, G. and Katz, S. G. 2006. Peripheral angioplasty with same-day discharge in patients with intermittent claudication. *Journal of Vascular Surgery* 44: 115-8.

Alex, J. R., Kamath, R. M., Gerald, W. and Fleisher, M. 2009. Analytical validation of the GeXP analyzer and design of a workflow for cancer-biomarker discovery using multiplexed gene-expression profiling. *Analytical and Bioanalytical Chemistry* 393: 1505-1511.

Alexandru, N., Popov, D. and Georgescu, A. 2012. Platelet dysfunction in vascular pathologies and how can it be treated. *Thrombosis Research* 129: 116-126.

Ambrose, J. A. and Barua, R.S. 2004. The pathophysiology of cigarette smoking and cardiovascular disease. *Journal of the American College of Cardiology* 43: 1731-1737.

Ameno, S., Ameno, K., Kinoshita, H., Tanaka, N. and Ijiri, I. 1997. Lewis genotyping by the PCR-RFLP method in a Japanese population and its

evaluation in forensic analysis. *International Journal of Legal Medicine* 110: 232-234.

Anderson, J. L., King, G. J., Bair, T. L., Elmer, S. P., Muhlestein, J. B., Habashi, J., Mixson, L. and Carlquist, J. F. 1999. Association of lipoprotein lipase gene polymorphisms with coronary artery disease. *Journal of the American College of Cardiology* 33: 1013-1020.

Arnett, D. K. 2007. Summary of the American Heart Association's scientific statement on the relevance of genetics and genomics for prevention and treatment of cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 27: 1682-1686.

Arnett, D. K., Baird, A. E., Barkley, R. A., Basson, C. T., Boerwinkle, E., Ganesh, S. K., Herrington, D. M., Hong, Y., Jaquish, C., McDermott, D. A. and O'Donnell, C. J. 2007. Relevance of genetics and genomics for prevention and treatment of cardiovascular disease: A scientific statement from the American Heart Association Council on Epidemiology and Prevention, the Stroke Council, and the Functional Genomics and Translational Biology Interdisciplinary working group. *Circulation* 115: 2878-2901.

Assmann, G., and Gotto Jr, A. M. 2004. HDL cholesterol and protective factors in atherosclerosis. *Circulation* 109(23) (suppl 1): III-8.

Auro, K., Komulainen, K., Alanne, M., Silander, K., Peltonen, L., Perola, M. and Salomaa, V. 2006. Thrombomodulin gene polymorphisms and haplotypes and the risk of cardiovascular events. *Arteriosclerosis Thrombosis Vascular Biology* 26: 942-947.

Austin, M. A., Hutter, C. M., Zimmern, R. L. and Humphries, S. E. 2004. Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: A HuGE Prevalence Review. *American Journal of Epidemiology* 160: 407-420.

Ayyobi, A. F., McGladdery, S. H., Chan, S., Mancini, G. B. J., Hill, J. S., and Frohlich, J. J. 2004 Lecithin: cholesterol acyltransferase (LCAT) deficiency and risk of vascular disease: 25 year follow-up. *Atherosclerosis* 177: 361-366.

Ballotta, E., Giau, G. D., Renon, L., Narne, S., Saladini, M., Abbruzzese, E. and Meneghetti, G. 1999. Cranial and cervical nerve injuries after carotid endarterectomy: A prospective study. *Surgery* 125: 85-91.

Baroni, M. G., D'Andrea, M. P., Montali, A., Pannitteri, G., Barillà, F., Campagna, F., Mazzei, E., Lovari, S., Seccareccia, F., Campa, P. P., Ricci, G., Pozzilli, P., Urbinati, G. and Arca, M. 1999. A common mutation of the insulin receptor substrate-1 gene is a risk factor for coronary artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 19: 2975-2980.

Bassuk, S. S. and Manson, J. E. 2005. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *Journal of Applied Physiology* 99: 1193-1204.

Bays, H. E. 2007. Safety considerations with omega-3 fatty acid therapy. *American Journal of Epidemiology* 99(6) (suppl): 35-43.

Beauchamp, N. J., van Achterberg, T. A. E., Engelse, M. A., Pannekoek, H. and de Vries, C. J. M. 2003. Gene expression profiling of resting and activated vascular smooth muscle cells by serial analysis of gene expression and clustering analysis. *Genomics* 82: 288–299.

Bellini, M. F., Cadamuro, A. C. T., Succi, M., Proença, M. A., and Silva, A. E. 2012. Alterations of the TP53 Gene in Gastric and Esophageal Carcinogenesis. *Journal of Biomedicine and Biotechnology* Article ID 891961, 13 pages.

Blann, A. D., Amiral, J. and McCollum, C.N. 1997. Prognostic value of increased soluble thrombomodulin and increased soluble E-selectin in ischaemic heart disease. *European Journal of Haematology* 59: 115-20.

Block, G., Jensen, C. D., Dalvi, T. B., Norkus, E. P., Hudes, M., Crawford, P. B., Holland, N., Fung, E. B., Schumacher, L. and Harmatz, P. 2009. Vitamin C treatment reduces elevated C-reactive protein. *Free Radical Biology & Medicine* 46: 70-77.

Bonafe´, M., Salvioli, S., Barbi, C., Trapassi, C., Tocco, F., Storci, G., Invidia, L., Vannini, I., Rossi, M., Marzi, E., Mishto, M., Capri, M., Olivieri, F., Antonicelli, R., Memo, M., Uberti, D., Nacmias, B., Sorbi, S., Monti, D. and Francesch, C. 2004. The different apoptotic potential of the p53 codon 72 alleles increases with age and modulates in vivo ischaemia-induced cell death. *Cell Death and Differentiation* 11: 962-973.

Caamano, J., Saavedra, N., Jaramillo, P. C., Lanas, C., Lanas, F. and Salazar, L. A. 2011. *TP53* codon 72 polymorphism is associated with coronary artery disease in Chilean subjects. *Medical Principles and Practice* 20: 171-176.

Callow, A. D. 2006. Cardiovascular disease 2005 — the global picture. *Vascular Pharmacology* 45: 302-307.

Castano, G., Maria L. Arruzazabala, M.L., Fernandez, L., Mas, R., Carbajal, D., Molina, V., IIInait, J., Mendozal, S., Gmez, R., Mesa, M. and Fernandez, J. 2006. Effects of combination treatment with policosanol and omega-3 fatty acids on platelet aggregation" A randomized, double-blind clinical study. *Current Therapeutic Research, Clinical and Experimental* 67: 174-192.

Chahil, J. K., Lye, S. H., Bagali, P. G. and Alex, L. 2012. A novel pathogenic variant of the LDLR gene in the Asian population and its clinical correlation with familial hypercholesterolemia. *Molecular Biology Reports* 39: 7831-7838.

Chan, S., Chen, J., Li, Y., Lin, L. and Tsai, L. 2006. Increasing post-event plasma thrombomodulin level associates with worse outcome in survival of acute coronary syndrome. *International Journal of Cardiology* 111: 280-285.

Chang, C. and Meyerowitz, E. M. 1991. Plant genome studies: restriction fragment length polymorphism and chromosome mapping information. *Current Opinion in Genetics and Development* 1: 112-118.

Chapman, M. J., Redfern, J. S., McGovern, M. E. and Giral, P. 2010. Niacin and fibrates in atherogenic dyslipidemia: Pharmacotherapy to reduce cardiovascular risk. *Pharmacology & Therapeutics* 126: 314-345.

Chen, G., Gharib, T. G., Huang, C., Taylor, J. M. G., Misek, D. E., Kardia, S. L. R., Giordano, T. J., Iannettoni, M. D., Orringer, M. B., Hanash, S. M. and Beer, D. G. 2002. Discordant Protein and mRNA Expression in Lung Adenocarcinomas. *Molecular & Cellular Proteomics* 1: 304-313.

Chen, Y., Rollins, J., Paigen, B.and Wang, X. 2007. Genetic and genomic insights into the molecular basis of atherosclerosis. *Cell Metabolism* 6: 164-179.

Cheng, Y., Chen, K., Wang, C., Chand, S., Change, W. and Chen, J. 2005. Secular trends in coronary heart disease mortality, hospitalization rates, and major cardiovascular risk factors in Taiwan, 1971–2001. *International Journal of Cardiology* 100: 47-52.

Cheung, M.C., Zhao, X., Chait, A., Albers, J. J. and Brown, B. G. 2001. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arteriosclerosis, Thrombosis, and Vascular Biology* 21: 1320-1326.

Chhatriwalla, A. K., Nicholls, S. J., Wang, T. H., Wolski, K., Sipahi, I., Crowe, T., Schoenhagen, P., Kapadia, S., Tuzcu, E. M. and Nissen, S. E. 2009. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. *Journal of the American College of Cardiology* 53: 1110-1115.

Cole, J. W., Roberts, S. C., Gallagher, M., Giles, W. H., Mitchell, B. D., Steinberg, K. K., Wozniak, M. A., Macko, R. F Reinhart, L. J. and Kittner, S. J. 2004. Thrombomodulin Ala455Val Polymorphism and the risk of cerebral infarction in a biracial population: the Stroke Prevention in Young Women Study. *BioMedCentral Neurology* 4(21): 1-7.

Coppe´e, J. 2008. Do DNA microarrays have their future behind them? *Microbes and Infection* 10: 1067-1071.

Cormack, F., Shipolini, A., Awad, W. I., Richardson, C., McCormack, D. J., Colleoni, L., Underwood, M., Baldeweg, T. and Hogan, A. M. 2012. A meta-analysis of cognitive outcome following coronary artery bypass graft Surgery. *Neuroscience and Biobehavioral Reviews* 36: 2118-2129.

Corsini, A., Raiteri, M., Soma, M. R., Bernini, F., Fumagalli, R. and Paoletti, R. 1995. Pathogenesis of atherosclerosis and the role of 3-Hydroxy.3.Methylglutaryl Coenzyme A Reductase inhibitors. *American Journal of Cardiology* 76: 21A-28A.

Costa, K.A. and Guillo, L. A. 2012. TP53 codon 72 polymorphism in pigmentary phenotypes. *Journal of Biosciences* 37(1): 33-39.

Crowther, M. A. 2005. Pathogenesis of atherosclerosis. *ASH Education Program Book*, 2005(1), 436-441.

Cybulsky, M. I., Iiyama, K., Li, H., Zhu, S., Chen, M., Iiyama, M., Davis, V., Gutierrez-Ramos, J., Connelly, P. W. and Milstone, D. S. 2001. A major role for VCAM-1, but not ICAM-1, in early atherosclerosis. *Journal of Clinical Investigation* 107: 1255-1262.

Damani, S. B. and Topol, E. J. 2007. Future use of genomics in coronary artery disease. *Journal of the American College of Cardiology* 50(20): 1993-1940.

Dantas, A. P., Jimenez-Altayo, F. and Vila, E. 2012. Vascular aging: facts and factors. *Frontiers in Physiology* 3(325): 1-2.

Darde, M. 2004. Genetic analysis of the diversity in *Toxoplasma gondii*. *Annali dell'Istituto Superiore di Sanità* 40(1): 57-63.

de Waard, V., van den Berg, B. M. M., Veken, J., Schultz-Heienbrok, R., Pannekoek, H. and van Zonneveld, A. 1999. Serial analysis of gene expression to assess the endothelial cell response to an atherogenic stimulus. *Gene* 226: 1-8.

Deo, R., Khera, A., McGuire, D. K., Murphy, S. A., Neto, J. D. P. M., Morrow, D. A. and de Lemos, J. A. 2004. Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. *Journal of the American College of Cardiology* 44:1812–-1818.

Destenaves, B. and Thomas, F. 2000. New advances in pharmacogenomics. *Current Opinion in Chemical Biology* 4: 440-444.

Drew, J. E., Mayer, C., Farquharson, A. J., Young, P. and Barrera, L. N. 2011. Custom design of a GeXP Multiplexed Assay used to assess expression profiles of inflammatory gene targets in normal colon, polyp, and tumor tissue. *Journal of Molecular Diagnostics* 13: 233-242.

Dumont, P., Leu, J. I., Pietra, A. C. D., George, D. L. and Murphy, M. 2003. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nature Genetics* 33: 357-365.

Eickelberg, O. and Morty, R. E. 2007. Transforming growth factor β/bone morphogenic protein signalling in pulmonary arterial hypertension: Remodeling revisited. *Trends Cardiovascular Medicine* 17: 263-269.

Endo, A. 1992. The discovery and development of HMG-CoA reductase inhibitors. *Journal of Lipid Research* 33: 1569-1582.

Enriquez, J. R., Pratap, P., Zbilut, J. P., Calvin, J. E. and Volgman, A. S. 2008. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, β-blockers, or statins. *Gender Medicine* 5(1): 53-61.

Erhardt, L. 2009. Cigarette smoking: An undertreated risk factor for cardiovascular disease. *Atherosclerosis* 205: 23-32.

Falk, E. 2006. Pathogenesis of atherosclerosis. *Journal of the American College of Cardiology* 47: 7-12.

Fallah, S., Seifi, M., Ghasemi, A., Firoozrai, M. and Samadikuchaksaraei, A. 2010. Matrix metalloproteinase-9 and paraoxonase 1 Q/R192 gene polymorphisms and the risk of coronary artery stenosis in Iranian subjects. *Journal of Clinical Laboratory Analysis* 24: 305-310.

Farpour-Lambert, N. J., Aggoun, Y., Marchand, L. M., Martin, X. E., Herrmann, F. R. and Beghetti, M. 2009. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *Journal of the American College of Cardiology* 54: 2396-2406.

Fernandez, B., Angele, M. K. and Koutang, C. 2011 Genetic polymorphisms of TP53 and FAS promoter modulate the progression of coronary artery disease after coronary artery bypass grafting: a gender-specific view. *Inflammation Research* 60: 439-445.

Fishbein, M. C. 2010. The vulnerable and unstable atherosclerotic plaque. *Cardiovascular Pathology* 19: 6-11.

Fortunato, G. and Taranto, M. D. D. 2007. Polymorphisms and the expression of genes encoding enzymes involved in cardiovascular diseases. *Clinica Chimica Acta* 381: 21-25.

Franchini, M., Peyvandi, F. and Mannucci, P. M. 2008. The genetic basis of coronary artery disease: From candidate genes to whole genome analysis. *Trends in Cardiovascular Medicine* 18: 157-162.

Fukuda, D., Shimada, K., Tanaka, A., Kusuyama, T., Yamashita, H., Ehara, S., Nakamura,Y., Kawarabayashi, T., Iida, H., Yoshiyama, M. and Yoshikawa, J. 2006. Comparison of levels of serum matrix metalloproteinase-9 in patients with acute myocardial infarction versus unstable angina pectoris versus stable angina pectoris. *American Journal of Cardiology* 97: 175−80.

Galis, Z. S. and Khatri, J. J. 2002. Matrix metalloproteinases in vascular remodeling and atherogenesis : The good, the bad, and the ugly. *Circulation Research* 90: 251-262.

Gaur, R., Azam, S., Jeena, G., Khan, A. W., Choudhary, S., Jain, M., Yadav, G., Tyagi, A. K., Chattopadhyay, D. and Bhatia, S. 2012. High-Throughput SNP discovery and genotyping for constructing a saturated linkage map of chickpea (*Cicer arietinum L.*). *DNA Research* 19: 357-373.

Gerdes, L. U., Gerdes, C., Kervinen, K., Savolainen, M., Klausen, I. C., Hansen, P.S., Kesaniemi, Y. A. and Fargeman, O. 2000. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction: a substudy of the Scandinavian simvastatin survival study. *Circulation* 101: 1366-1371.

Gibbons, G. H., Choong, C. L., Goodarzi, M. O., Rotter, J. I., Hsueh, W. A., Siragy, H. M., Pratt, R. and Dzau, V. J. 2004. Genetic markers: Progress and potential for cardiovascular disease. *Circulation* 109(25) (suppl 1): IV-47.

Glantz, S. A. and Parmley, W. W. 1991. Passive smoking and heart disease. Epidemiology, physiology, and biochemistry. *Circulation* 83(1): 1-12.

Gönül, N., Kadioglu, E., Kocabaş, N. A., Özkaya,M., Karakaya, A. E. and Karahalil, B. 2012. The role of GSTM1, GSTT1, GSTP1, and OGG1 polymorphisms in type 2 diabetes mellitus risk: A case–control study in a Turkish population. *Gene* 505: 121-127.

Gordon, L. B., Harten, I. A., Patti, M. E. and Lichtenstein, A. H. 2005. Reduced adiponectin and HDL cholesterol without elevated C-reactive protein: Clues to the biology of premature atherosclerosis in hutchinson-gilford progeria syndrome. *Journal of Pediatrics* 146: 336-341.

Graham, I. M. and O'Callaghan, P. 2002. Vitamins, Homocysteine and Cardiovascular Risk. *Cardiovascular Drugs and Therapy* 16: 383-389.

Gu, L., Okada, Y., Clinton, S. K., Gerard, C., Sukhova, G. K., Libby, P. and Rollins, B. J. 1998. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor–deficient mice. *Molecular Cell* 2: 275-281.

Hammad, S. M., Seigel, H. S. and Marks, H. L. 1998. Total cholesterol, total triglycerides, and cholesterol distribution among lipoproteins as predictors of atherosclerosis in selected lines of Japanese Quail. *Comparative Biochemistry* and *Physiology* 199(2): 485-492.

Helgadottir, A., Gretarsdottir, S., Clair, D. S., Manolescu, A., Cheung, J., Thorleifsson, G., Pasdar, A., Grant, S. F. A., Whalley, L. J., Hakonarson, H., Thorsteinsdottir, U., Kong, A., Gulcher, J., Stefansson, K. and MacLeod, M. J. 2005. Association between the gene encoding 5-lipoxygenase–activating protein and stroke replicated in a Scottish population. *American Journal of Human Genetics* 76: 505-509.

Horne, B. D., Camp, N. J., Carlquist, J. F., Muhlestein, J. B., Kolek, M. J., Nicholas, Z. P. and Anderson, J. L. 2007. Multi-polymorphism association of 7 matrix metalloproteinase and tissue inhibitor metalloproteinase genes with myocardial infarction and angiographic coronary artery disease. *American Heart Journal* 154: 751-758.

Hou, L., Huang, J., Lu, X., Wang, L., Fan, Z. and Gu, D. 2009. Polymorphisms of tumor necrosis factor alpha gene and coronary heart disease in a Chinese Han population: Interaction with cigarette smoking. *Thrombosis Research* 123: 822-826.

Hovingh, G. K., Hutten, B. A., Holleboom, A. G., Petersen, W., Rol, P., Stalenhoef, A., Zwinderman, A. H., de Groot, E., Kastelein, J..J.P. and Kuivenhoven, J. A. 2005. Compromised LCAT function is associated with increased atherosclerosis. *Circulation* 112: 879-884.

Huang, W., Moriyama, K., Koga, T., Hua, H., Ageta, M., Kawabata, S., Mawatari, K., Imamura, T., Eto, T., Kawamura, M., Teramoto, T. and Sasaki, J. 2001. Novel mutations in ABCA1 gene in Japanese patients with Tangier disease and familial high density lipoprotein de¢ciency with coronary heart disease. *Biochimica et Biophysica Acta* 1537: 71-78.

Humphries, S. E. and Ordovas, J. M. 2001. Genetics and atherosclerosis: Broadening the horizon. *Atherosclerosis* 154: 517-519.

Hur, S. J., Du, M., Nam, K., Williamson, M. and Ahn, D. U. 2005. Effect of dietary fats on blood cholesterol and lipid and the development of atherosclerosis in rabbits. *Nutrition Research* 25: 925-935.

Isbir, T., Yaylim, I., Arikan, S., Kaytan, E., Karsidag, T., Bayrak, S. S. and Çamlica, H. 2002. Close correlation between restriction fragment length polymorphism of L-*myc* gene and susceptibility to gastric cancer. *Cancer Detection and Prevention* 26: 454-457.

Ismail, M., Al-Naqeep. G. and Chan, K. W. 2010. Nigella sativa thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. *Free Radical Biology & Medicine* 48: 664-672.

Jefferis, B. J., Whincup, P., Welsh, P., Wannamethee, G., Rumley, A., Lennon, L., Thomson, A., Lawlor, D., Carson, C., Ebrahim, S. and Lowe, G. 2010. Prospective study of matrix metalloproteinase-9 and risk of myocardial infarction and stroke in older men and women. *Atherosclerosis* 208: 557–63.

Jekel, J. F., Katz, D. L. and Elmore, J. G. (2001). Epidermiology, biostatistics, and preventive medicine, second edition.

Jeong, Y., Ishikawa, K., Someya, Y., Hosoda, A., Yoshimi, T., Yokoyama, C., Kiryu-Seo, S., Kang, M., Tchibana, T., Kiyama, H., Fukumura, T., Kim, D. and Saeki, S. 2010. Molecular characterization and expression of the low-density lipoprotein receptor-related protein-10, a new member of the LDLR gene family. *Biochemical and Biophysical Research Communications* 391: 1110-1115.

Jia, X., Ju, H., Yang, L. and Tian, Y. 2012. A novel multiplex polymerase chain reaction assay for profile analyses of gene expression in peripheral blood. *Cardiovascular Disorders* 12(51): 1-9.

Kaaman, M., Ryde´n, M., Axelsson, T., Nordstro¨m, E., Sicard, A., Bouloumie´, A., Langin, D., Arner, P. and Dahlman, I. 2006 *ALOX5AP* expression, but not gene haplotypes, is associated with obesity and insulin resistance. *International Journal of Obesity* 30: 447-452.

Kakihara, F., Kurebayashi, Y., Tojo, Y., Tajima, H., Hasegawa, S. and Yohda, M. 2005. MagSNiPer: A new single nucleotide polymorphism typing method based on single base extension, magnetic separation, and chemiluminescence. *Analytical Biochemistry* 341:77-82.

Kang, W. U., Jeong, M. H., Ahn, Y. K., Kim, J. H., Chae, S. C., Kim, Y. J., Hur, S. H., Seong, I. W., Hong, T. J., Choi, D. H., Cho, M. C., Kim, C. J., Seung, K. B., Chung, W. S., Jang, Y. S., Rha, S. W., Bae, J. H., Cho, J. G. and Park, S. J. 2010. Obesity paradox in Korean patients undergoing primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. *Journal of Cardiology* 55: 84-91.

Kekalainen, P., Sarlund, H., Pyorala, K. and Laakso, M. 1996. Family history of coronary heart disease is a stronger predictor of coronary heart disease morbidity and mortality than family history of non-insulin dependent diabetes mellitus. *Atherosclerosis* 123: 203-213.

Khoo, K. L., Tan, H. and Khoo, T. H. 1991. Cardiovascular mortality in Peninsular Malaysia: 1950-1989. *Medical Journal of Malaysia* 46(1): 7-20.

Khor, G. L. 2001. Cardiovascular epidemiology in the Asia–Pacific region. *Asia Pacific Journal of Clinical Nutrition* 10(2): 76–80.

Klerk, M., Verhoef, P., Clarke, R., Blom, H. J., Kok, F. J. and Schouten, E. G. 2002. *MTHFR*677C→T Polymorphism and the risk of coronary heart disease. *Journal of the American Medical Association* 288: 2023-2031.

Kluijtmans, L. A. J., van den Heuvel, L. P. W. J., Boers, G. H. J., Frosst, P., Stevens, E. M. B., van Oost, B. A., den Heijer, M., Trijbels, F. J. M., Rozen, R. and Blom, H. J. 1996. Molecular genetic analysis in mild hyperhomocysteinemia: A common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. *American Journal of Human Genetics* 58: 35-41.

Knipp, S. C., Matatko, N., Wilhelm, H., Schlamann, M., Thielmann, M., Lösch, C., Diener, H. C. and Jakob, H. 2008. Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. *The Annals of Thoracic Surgery* 85(3): 872-879.

Kockx, M. M. and Herman, A. G. 2000. Apoptosis in atherosclerosis: beneficial or detrimental? *Cardiovascular Research* 45: 736-746.

Kovacic, S. and Bakran, M. 2012. Genetic susceptibility to atherosclerosis. *Stroke Research and Treatment* 2012.

Kovacs, P., Hanson, R. L., Lee, Y. H., Yang, X., Kobes, S., Permana, P. A., Bogardus, C. and Baier, L. J. 2003 The role of insulin receptor substrate-1 gene (IRS1) in type 2 diabetes in Pima Indians. *Diabetes* 52: 3005-3009.

Kruger, W. D., Evans, A. A., Wang, L., Malinow, M. R., Duell, P. B., Anderson, P. H., Block, P. C., Hess, D. L., Graf, E. E. and Upson, B. 2000. Polymorphisms in the *CBS* gene associated with decreased risk of coronary artery disease and increased responsiveness to total homocysteine lowering by folic acid. *Molecular Genetics and Metabolism* 70: 53-60.

Kurella, M., Hsiao, L., Yoshida, T., Randall, J. D., Chow, G., Sarang, S. S., Jensen, R. V. and Gullans, S. R. 2001. DNA microarray analysis of complex biologic processes. *Journal of the American Society and Nephrology* 12: 1072-1078.

Kvan, E., Pettersen, K. I., Sandvik, L. and Aasmund Reikvam, A. 2007. High mortality in diabetic patients with acute myocardial infarction: Cardiovascular co-morbidities contribute most to the high risk. *International Journal of Cardiology* 121: 184-188.

Lakatta, E. G. 2007. Central arterial aging and the epidemic of systolic hypertension and atherosclerosis. *Journal of the American Society of Hypertension* 1(5): 302-340.

Laporan Perangkaan Kemalangan Jalan Raya Malaysia (Statistical Report of Road Accident). 2008. Polis Diraja Malaysia Cawangan Trafik Kuala Lumpur.

Laporan Perangkaan Kemalangan Jalan Raya Malaysia (Statistical Report of Road Accident). 2009. Polis Diraja Malaysia Cawangan Trafik Kuala Lumpur.

Laporan Perangkaan Kemalangan Jalan Raya Malaysia (Statistical Report of Road Accident). 2010. Polis Diraja Malaysia Cawangan Trafik Kuala Lumpur.

Laszik, Z. G., Zhou, X. J., Ferrell, G. L., Silva, F. G. and Esmon, C. T. 2001. Down-regulation of endothelial expression of endothelial cell protein C receptor and thrombomodulin in coronary atherosclerosis. *American Journal of Pathology* 159: 797-802.

Laufs, U., Wassmann, S., Czech, T., Münzel, T., Eisenhauer, M., Böhm, M. and Nickenig, G. 2005. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 25: 809-814.

Lavie, C. J., Milani, R. V. and Ventura, H. O. 2009. Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology* 53: 1925-1932.

Law, M. R. and Wald, N. J. 2003. Environmental tobacco smoke and ischemic heart disease. *Progress in Cardiovascular Diseases* 46(1): 31-38.

Law, M. R., Morris J. K. and Wald, N. J. 1997. Environmental tobacco smoke exposure and ischemic heart disease: An evaluation of the evidence. *British Medical Journal* 315: 973-988.

Laws, P. E., Spark, J. I., Cowled, P. A. and Fitridge, R. A. 2004. The role of statins in vascular disease. *European Journal of Vascular and Endovascular Surgery* 27: 6-16.

Leander, K., Hallqvist, J., Reuterwall, C., Ahlbom, A. and de Faire, U. 2001. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEEP). *Epidemiology* 12: 215-221.

Lechner, D., Lathrop, G. M. and Gut, I. G. 2001. Large-scale genotyping by mass spectrometry: experience, advances and obstacles. *Current Opinion in Chemical Biology* 6: 31-38.

Lee, H. and Lee, J. W. 1999. Statistical methods in criminal inference using DNA fingerprints. *Computational Statistics & Data Analysis* 32: 47-67.

Lee, S., Hou, M., Hsieh, P., Wu, S., Hou, L. A., Ma, H., Tsai, S. and Tsai, L. 2008. A case–control study of the HER2 Ile655Val polymorphism and risk of breast cancer in Taiwan. *Clinical Biochemistry* 41: 121-125.

Lee, S., Shin, D. and Jang, Y. 2009. Personalized medicine in coronary artery disease: Insights from genomic research. *Korean Circulation Journal* 39: 129-137.

Leigh, S. E. A., Foster, A. H., Whittall, R. A., Hubbart, C. S. and Humphries, S. E. 2008. Update and analysis of the University College London low density lipoprotein receptor Familial Hypercholesterolemia database. *Annals of Human Genetics* 72: 485-498.

Lesauskaite, V., Ivanoviene, L. and Valanciute, A. 2003 Programmed cellular death and atherogenesis: from molecular mechanisms to clinical aspects. *Medicina* 39(6): 529-534.

Levine, A. J., Hu, W. and Feng, Z. 2006. The P53 pathway: what questions remain to be explored? *Cell Death and Differentiation* 13: 1027-1036.

Li, J., Smyth, P., Flavin, R., Cahill, S., Denning, K., Aherne, S., Guenther, S. M., O'Leary, J. J. and Sheils, O. 2007. Comparison of miRNA expression patterns using total RNA extracted from matched samples of formalin-fixed paraffin-embedded (FFPE) cells and snap frozen cells. *BMC Biotechnology* 7(1): 36.

Li, Y., Li, Z., Zhang, X., Yan, C., Kang, J., Liang, Z., Liu, S., Feng, X. and Han, Y. Association of *ALOX5AP* haplotypes with susceptibility to coronary artery disease in a Chinese Han population. *European Journal of Internal Medicine* 23: e119-e123.

Liang, L., Wong, N. D., Shi, P., Zhao, L., Wu, L., Xie, G. and Wu, Y. 2009. Cross-sectional and longitudinal association of cigarette smoking with carotid atherosclerosis in Chinese adults. *Preventive Medicine* 49: 62–67.

Liang, P. and Pardee, A. B. 1998. Differential Display: A General Protocol. *Molecular Biotechnology* 10: 261-267.

Liao, P. and Lee, K. H. 2010. From SNPs to functional polymorphism: The insight into biotechnology applications. *Biochemical Engineering Journal* 49: 149-158.

Lievers, K. J. A., Kluijtmans, L. A. J. and Blom, H. J. 2003. Genetics of hyperhomocysteinaemia in cardiovascular disease. *Annals of Clinical Biochemistry* 40: 46-59.

Lloyd-Jones, D., Adams, R. J., Brown, T. M., Carnethon, M., Dai, S., Simone, G. D., Ferguson, T. B., Ford, E., Furie, K., Gillespie, C., Go, A., Greenlund, K., Haase, N., Hailpern, S., Ho, P, M., Howard, V., Kissela., B., Kittner, S., Lackland, D., Lisabeth, L., Marelli, A., McDermott, M. M., Meigs, J., Mozaffarian, D., Mussolino, M., Nichol, G., Roger, V. L., Rosamond, W., Sacco, R., Sorlie, P., Stafford, R., Thom, T., Wasserthiel-Smoller, S., Wong, N. D. and Wylie-Rosett, J. 2010. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 121(7): 948.

Loftus, I. M., Naylor, A. R., Bell, P. R. F. and Thompson, M. M. 2002 Matrix metalloproteinases and atherosclerotic plaque instability. *British Journal of Surgery* 89: 680-694.

López-Cancio, E., Doradoa, L., Millána, M., Revertéa, S., Su˜nola, A., Massuetb, A., Galánc, A., Alzamorad, M. T., Perad, G., Toránd, P., Dávalosa, A. and Arenillase, J. F. 2012. The barcelona-asymptomatic intracranial atherosclerosis (AsIA) study: Prevalence and risk factors. *Atherosclerosis* 221: 221-225.

Lusis, A. J. 2003. Genetic factors in cardiovascular disease: 10 questions. *Trends in Cardiovascular Medicine* 13: 309-316.

Lusis, A. J. 2012. Genetics of atherosclerosis. *Trends in Genetics* 28(6): 267-275.

Lusis, A. J., Fogelman, A. M. and Fonarow, G. C. 2004. Genetic basis of atherosclerosis: Part I : New genes and pathways. *Circulation* 110: 1868-1873.

Mager, A., Koren-Morag, N., Shohat, M., Harell, D. and Battler,A. 2005. Family history, plasma homocysteine, and age at onset of symptoms of myocardial ischemia in patients with different methylenetetrahydrofolate reductase genotypes. *American Journal of Cardiology* 95: 1420-1424.

Maier, J. A. M., Malpuech-Bruge`re, C., Zimowska, W., Rayssiguier, Y. and Mazur, A. 2004. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis. *Biochimica et Biophysica Acta* 1689: 13-21.

Mallat, Z. and Tedgui, A. 2000. Apoptosis in the vasculature: mechanisms and functional importance. *British Journal of Pharmacology* 130: 947-962.

Malloy, S. I., Altenburg, M. K., Knouff, C., Lanningham-Foster, L., Parks, J. S. and Maeda, N. 2004. Harmful effects of increased LDLR expression in mice with human *APOEε4* but not *APOε3*. *Arteriosclerosis, Thrombosis, and Vascular Biology* 24: 91-97.

Malloy, S. I., Altenburg, M. K., Knouff, C., Lanningham-Foster, L., Parks, J. S. and Maeda, N. 2004. Harmful effects of increased *LDLR* expression in mice with human *APOE*4* but not *APOE*3*. *Arteriosclerosis Thrombosis Vascular Biology* 24: 91-97.

Mamotte, C. D. S., Burke, V., Taylor, R. R. and van Bockxmeer, F. M. 2002. E vidence of reduced coronary artery disease risk for apolipoprotein ε2/3 heterozygotes. *European Journal of Internal Medicine* 13: 250-255.

Mauray, A., Felgines, C., Morand, C., Mazur, A., Scalbert, A. and Milenkovic, D. 2012. Bilberry anthocyanin-rich extract alters expression of genes related to atherosclerosis development in aorta of apo E-deficient mice. *Nutrition, Metabolism & Cardiovascular Diseases* 22: 72-80.

McMahan, C, A., Gidding, S. S. and McGrill, H. C. 2008. Coronary heart disease risk factors and atherosclerosis in young people. *Journal of Clinical Lipidology* 2: 118-126.

McPherson, R. and Davies, R. W. 2012. Inflammation and coronary artery disease: Insights from genetic studies. *Canadian Journal of Cardiology* 28(6): 662-666.

Mead, J. R., Cryer, A., and Ramji, D. P. 1999. Lipoprotein lipase, a key role in atherosclerosis?. *FEBS letters* 462(1): 1-6.

Mendis, S., Shepherd, J., Packard, C. J. and Gaffney, D. 1991. Restriction fragment length polymorphisms in the Apo B gene in relation to coronary heart disease in a Southern Asian population. *Clinica Chimica Acta* 196: 107-118.

Meyer, M. A., Haas, E. and Barton, M. 2008. Need for research on estrogen receptor function: Importance for postmenopausal hormone therapy and atherosclerosis. *Gender Medicine* 5(suppl. A): 19-33.

Mezaki, T., Matsubara, T., Hori, T., Higuchi, K., Nakamura, A., Nakagawa, I., Imas, S., Ozaki, K., Tsuchida, K., Nasuno, A., Tanaka, T., Kubota, K., Nakano, M., Miida, T. and Aizawa, Y. 2003. Plasma levels of soluble thrombomodulin, C-reactive protein, and serum amyloid A protein in the atherosclerotic coronary circulation. *Japanese Heart Journal* 44: 601-12.

Monraats, P. S., and Jukema, J. W. 2011. The Pharmacogenetics of Atherosclerosis. *Clinical Cardiogenetics* 353-367.

Morgan, A. R., Zhang, B., Tapper, W., Collins, A. and Ye, S. 2003. Haplotypic analysis of the *MMP-9* gene in relation to coronary artery disease. *Journal of Molecular Medicine* 81: 321-326.

Nakagawa, I., Matsubara, T., Hori, T., Imas, S., Ozaki, K., Mezaki, T., Nasuno, A., Kubota, K., Nakano, M., Yamazoe, M. and Aizawa, Y. 2001. Significance of soluble thrombomodulin in the coronary circulation of patients with coronary artery disease. *Journal of Cardiology* 8: 145-52.

Nanni, L., Romualdi, C., Maseri, A. and Lanfranchi, G. 2006. Differential gene expression profiling in genetic and multifactorial cardiovascular diseases. *Journal of Molecular and Cellular Cardiology* 41: 934-948.

Nasser, T. K., Mohler, E. R., Wilensky, R. L., Hathaway, D. R. 1995. Peripheral vascular complications following coronary interventional procedures. *Clinical Cardiology* 18: 609-614.

Newby, A. C. 2005. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. *Physiological Reviews* 85: 1-31.

Nishiyama, A., Shikata, C., Kimura, N., Imanishi, A., Hirai, N., Ohta, M. and Takeda, N. 2005. Risk factors for coronary artery sclerosis in patients with diabetes. *Experimental & Clinical Cardiology* 10(2): 108-110.

Nissen, S. E., Nicholls, S. J., Sipahi, I., Libby, P., Raichlen, J. S., Ballantyne, C. M., Davignon, J., Erbel, R., Fruchart, J. C., Tardif, J., Schoenhagen, P., Tim Crowe, Cain, V., Wolski, K., Goormastic, M. and Tuzcu, E. M. 2006. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. *Journal of the American Medical Association* 295: 1556-165.

Nordlie, M. A., Wold, L. E. and Kloner, R. A. 2005. Genetic contributors toward increased risk for ischemic heart disease. *Journal of Molecular and Cellular Cardiology* 39: 667–679.

Nowotny, P., Kwon, J. M. and Goate, A. M. 2001. SNP analysis to dissect human traits. *Current Opinion in Neurobiology* 11: 637-641.

Ogasawara, K., Inoue, T., Kobayashi, M., Endo, H., Fukuda, T. and Ogawa, A. 2004. Intracerebral hemorrhage after carotid endarterectomy associated with asymptomatic perioperative cerebral ischemia detected by cerebral perfusion imaging: Case report. *Surgical Neurology* 62: 319 -323.

Ohayon, T., Gershoni-Baruch, R., Papa, M. Z., Menachem, T. D., Barzilai, S. E. and Friedman, E. 2005. The R72P P53 mutation is associated with familial breast cancer in Jewish women. *British Journal of Cancer* 92: 1144–1148.

Okrainec, K., Banerjee, D. K. and Eisenberg, M. J. 2004. Coronary artery disease in the developing world. *American Heart Journal* 148: 7-15.

Olivier, M., Hollstein, M. and Hainaut, P. 2010. TP53 mutations in human cancers: Origins, consequences, and clinical use. *Cold Spring Harbor Perspectives in Biology* 2(1): 001-008.

Omoigui, N. A., Califf, R. M., Pieper, K., Gordon Keeler, G., O'hanesian, M. A., Berdan, L. G., Mark, D. B., J. David Talley, J. D. and Topol, E. J. 1995. Peripheral vascular complications in the coronary angioplasty versus excisional atherectomy trial (CAVEAT-I). *Journal of the American College of Cardiology* 26: 922-30.

Orlandi, A., Bochaton-Piallat, M., Gabbiani, G. and Spagnoli, L. G. 2006. Aging, smooth muscle cells and vascular pathobiology: Implications for atherosclerosis. *Atherosclerosis* 188: 221-230.

Osada, M., D'Ambrose, M. and Balazs, I. 2003. Genotyping for single nucleotide polymorphism using a multiplex detection assay. *International Congress Series* 1239: 17-20.

Panjukanta, P., Nuotio, I., Terwilliger, J. D., Porkka, K. V. K., Ylitalo, K., Pihlajamaki, J., Suomalainen, A. J., Syvanen, A., Lehtimaki, T., Viikari, J. S. A., Laakso, M., Taskinen, M., Ehnholm, C. and Peltonen L. 1998. Linkage of familial combined hyperlipidaemia to chromosome 1q21-q23. *Nature Genetic* Vol 18 April 1998: 369-373.

Pasternak, R. C., Smith, S. C. and Bairey-Merz, C. N. 2002. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Journal of the American College of Cardiology* 40(3): 567-572.

Patino, W. D., Mian, O. Y., Kang, J., Matoba, S., Bartlett, L. D., Holbrook, B., Trout III, H. H., Kozloff, L. and Hwang, P. M. 2005. Circulating transcriptome reveals markers of atherosclerosis. *Proceedings of the National Academy of Sciences of the United States of America* 102(9): 3423-3428.

Pietsch, E. C., Humbey, O. and Murphy, M. E. 2006. Polymorphisms in the p53 pathway. *Oncogene* 25: 1602–1611.

Pisciotta, L., Cantafora, A., De Stefano, F., Langheim, S., Calandra, S. and Bertolini, S. 2002. A ''de novo'' mutation of the LDL-receptor gene as the cause of familial hypercholesterolemia. *Biochimica et Biophysica Acta* 1587: 7 - 11.

Qin, M., Wang, D., Huang, F., Nie, K., Qu, M., Wang, M., Shu, Y. and Ma, X. 2010. Detection of pandemic influenza A H1N1 virus by multiplex reverse transcription-PCR with a GeXP analyser. *Journal of Virological Methods* 168: 255–258.

Rai, A. J., Kamath, R. M. and Gerald, W. 2009. Analytical validation of the GeXP analyzer and design of a workflow for cancer-biomarker discovery using multiplexed gene-expression profiling. *Analytical and Bioanalytical Chemistry* 393: 1505-1511.

Rampal, L., Rampal, S., Azhar, M. Z. and Rahman, A. R. 2008. Prevalence, awareness, treatment and control of hypertension in Malaysia: A national study of 16,440 subjects. *Public Health* 122: 11–18.

Roberts, R. and Stewart, A. F. R. 2012. Genes and Coronary Artery Disease: Where Are We?. *Journal of the American College of Cardiology* 60: 1715-21.

Roberts, R., Stewart, A. F. R., Wells, G. A., Williams, K. A., Kavaslar, N. and McPherson, R. 2007. Identifying genes for coronary artery disease: An idea whose time has come. *Canadian Journal of Cardiology* 23(Suppl A): 7-15.

Ross, R. 1999. Atherosclerosis-An inflammatory disease. *The New England Journal of Medicine* 340 (2): 115-126.

Roy, H., Bhardwaj, S. and Yla-Herttuala, S. 2009. Molecular genetics of atherosclerosis. *Human Genetics* 125:467–491.

Rujijanto, A. 2007. The role of vascular smooth muscle cells on the pathologenesis of atherosclerosis. *Acta Medica Indonesiana (The Indonesian Journal of Internal Medicine)* 39(2): 86-92.

Saedi, M., Vaisi-Raygani, A., Khaghani, S., Shariftabrizi, A., Rezaie, M., Pasalar, P., Rahimi, Z. and Pourmotabbed, T. 2012. Matrix metalloproteinas-9 functional promoter polymorphism 1562C>T increased risk of early-onset coronary artery disease. *Molecular Biology Reports* 39: 555-562.

Salazar, L. A., Hirata, M. H., Giannini, S. D., Forti, N., Diament, J., Lima, T. M., Hirata, R. D. C. 2000. Seven DNA polymorphisms at the candidate genes of atherosclerosis in Brazilian women with angiographically documented coronary artery disease. *Clinica Chimica Acta* 300: 139–149.

Salek, L. and Marian, A. J. 1997. Genetic basis of coronary atherosclerosis. *Journal of Clinical Investigation* 100(8): 2115-2124.

Salomaa, V., Matei, C., Aleksic, N., Sansores-Garcia, L., Folsom, A. R., Juneja, H., Park, E. and Wu, K. K. 2001. Cross-sectional association of soluble thrombomodulin with mild peripheral artery disease; the ARIC study. *Atherosclerosis* 157: 309-314.

Sathasivam, S. 2012. Statin induced myotoxicity. *European Journal of Internal Medicine* 23: 317-324.

Schindler, C. 2010. Influences of diabetes on the development and progression of cardiovascular disease. *British Journal of Diabetes & Vascular Disease* 10: 54-56.

Schlesselmen, J. J. 1982. Case control studies. Design, Conduct, Analysis. Oxford: Universiti Press.

Schroeder, A. P. and Falk, E. 1995. Vulnerable and dangerous coronary plaques. *Atherosclerosis* 118(Suppl.): l41-149.

Seo, D., Ginsburg, G. S. and Goldschmidt-Clermont, P. J. 2006. Gene expression analysis of cardiovascular diseases: Novel insights into biology and clinical applications. *Journal of the American College of Cardiology* 48: 227-235.

Seo, D., Wang, T., Dressman, H., Herderick, E. E., Iversen, E. S., Dong, C., Vata, K., Milano, C. A., Rigat, F., Pittman, J., Nevins, J. R., West, M. and Goldschmidt-Clermont, P. J. 2004. Gene expression phenotypes of atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 24: 1922-1927.

Sewelam, N. I., Radwan, E. R., Andraos, A. W., Ibrahim, B. E. and Wilson, M. M. 2013. *The Egyptian Journal of Medical Human Genetics* 14: 143-148.

Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., Macfarlane, P. W., Mckillop, J. H. and Packard, C. J. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine* 333: 1301-1307.

Sianipar, N. F. 2003. Penggunaan marker RFLP (Restriction Fragment Length Polymorphism) dalam pemiliaan tanaman. *Makalah Pribadi*. Pengantar ke Falsafah Sains. Bogor: Program Pascasarjana, Institut Pertanian Bogor.

Sitia, S., Tomasoni, L., Atzeni, F., Ambrosio, G., Cordiano, C., A. Catapano, A., Tramontana, S., Perticone, F., Naccarato, P., Camici, P., Picano, E., Cortigiani, L., Bevilacqua, M., Milazzo, L., Cusi, D., Barlassina, C., Sarzi-Puttini, P. and Turiel, M. 2010. From endothelial dysfunction to atherosclerosis. *Autoimmunity Reviews* 9: 830–834.

Smith, M. A. C., Silva, M. D. A., Cendoroglo, M. S., Ramos, L. R., Araujo, L.M.Q., Labio, R. W., Burbano, R. R., Chen, E. S. and Payão, S. L. M. 2007. *TP53* codon 72 polymorphism as a risk factor for cardiovascular disease in a Brazilian population. *Brazilian Journal of Medical and Biological Research* 40: 1465-1472.

Speakman, J. R., Rance, K. A. and Johnstone, A. M. 2008. Polymorphisms of the *FTO* gene are associated with variation in energy intake, but not energy expenditure. *Obesity* 16: 1961–1965.

Stary, H. C., Chandler, A. B., Glagov, S., Guyton, J. R., Insull, W., Rosenfeld, J. M. E., Schaffer, S. A. C., Schwartz, J., Wagner, W. D. and Wissler, R. W. 1994. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arteriosclerosis, Thrombosis, and Vascular Biology* 14: 840-856.

Stone, J. R. 2012. Pathology of myocardial infarction, coronary artery disease, plaque disruption, and the vulnerable atherosclerotic plaque. *Diagnostic Histopathology*.

Stoneman, V. E. A. and Bennett, M. R. 2004. Role of apoptosis in atherosclerosis and its therapeutic implications. *Clinical Science* 107: 343-354.

Sukhova, G., Schonbeck, U., Rabkin, E., Shoen, F. J., Poole, R., Billinghurst, R. C. and Libby, P. 1999. Evidence for increased collagenolysis interstitial collagenases-1 and -3 in vulnerable human atheromatous plaques. *Circulation* 99: 2503-2509.

Tai, E. S., Poulton, R., Thumboo, J., Sy, R., Castillo-Carandang, N., Sritara, P., Adam, J. M. F., Sim, K. H., Fong, A., Wee, H. L. and Woodward, M. 2009. An update on cardiovascular disease epidemiology in South East Asia. Rationale and design of the LIFE course study in CARdiovascular disease Epidemiology (LIFECARE). *CVD Prevention and Control* 4: 93-102.

Tamargo, J., Caballero, R., Gómez, R., Núñez, L., Vaquero, M. and Delpón, E. 2007. Lipid-lowering therapy with statins, a new approach to antiarrhythmic therapy. *Pharmacology & Therapeutics* 114: 107-126.

Tamemoto, H., Ishikawa, S. and Kawakami, M. 2008. Association of the Glu298Asp polymorphism of the eNOS Gene with ischemic heart disease in Japanese diabetic subjects. *Diabetes Research and Clinical Practice* 80: 275-279.

Tang, Q. D., Wu, P. S., Hou, Y. Q., Huang, Z., Zhou, Z. J., Guo, Z. G., Xiu, J. C. and Wang, Y. G. 2009. Plasma matrix metalloproteinases-2 and -9 levels are elevated in patients with acute coronary syndrome and coronary chronic total occlusion. *Journal of Southern Medical University* 29: 1004-7.

Taskinen, M. R. 2009. Lipoprotein lipase in diabetes. *Diabetes/Metabolism Reviews* 3(2): 551-570.

Tayebjee, M. H., Lip, G. Y., Tan, K. T., Patel, J. V., Hughes, E. A. and MacFadyen, R. J. 2005. Plasma matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-2, and CD40 ligand levels in patients with stable coronary artery disease. *American Journal of Cardiology* 96: 339–45.

Temple, N. J. 1996. Dietary fats and coronary heart disease. *Biomedicine & Pharmacotherapy* 50: 261-268.

Tietjen, I., Hovingh, G. K., Singaraja, R., Radomski, C., McEwen, J., Chan, E., Mattice, M., Legendre, A., Kastelein, J, J. P. and Hayden, M. R. 2012. Increased risk of coronary artery disease in Caucasians with extremely low HDL cholesterol due to mutations in *ABCA1, APOA1,* and *LCAT*. *Biochimica et Biophysica Acta* 1821: 416-424.

Tost, J. and Gut, I. G. 2005. Genotyping single nucleotide polymorphisms by MALDI mass spectrometry in clinical applications. *Clinical Biochemistry* 38: 335–-350.

Toubanaki, D. K., Christopoulos, T. K., Ioannou, P. C. and Flordellis, C. S. 2009. High-throughput chemiluminometric genotyping of single nucleotide polymorphisms of histamine, serotonin, and adrenergic receptor genes. *Analytical Biochemistry* 385: 34–41.

Tousoulis, D., Briasoulis, A., Papageorgiou, N., Antoniades, C. and Stefanadis, C. 2008. Candidate gene polymorphisms and the 9p21 locus in acute coronary syndromes. *Trends in Molecular Medicine* 14(10): 441-449.

Trollope, A. F. and Golledge, J. 2011. Angiopoietins, abdominal aortic aneurysm and atherosclerosis. *Atherosclerosis* 214: 237–243.

Tveten, K., Strøm, T. B., Cameron, J., Holla, Ø. L., Berge, K. E. and Leren, T. P. 2012. Characterization of a naturally occurring degradation product of the LDL receptor. *Molecular Genetics and Metabolism* 105: 149–154.

Ueno, S., Ohki, R., Hashimoto, T., Takizawa, T., Takeuchi, K., Yamashita, Y., Ota, J., Choi, Y. L., Wada, T., Koinuma, K., Yamamoto, K., Ikeda, U., Shimada, K., and Mano, H. 2003. DNA microarray analysis of in vivo progression mechanism of heart failure. *Biochemical and Biophysical Research Communications* 307: 771–777.

van Mook, W. N. K. A., Rennenberg, R. J. M. W., Schurink, G. W., van Oostenbrugge, R. J., Mess, W. H., Hofman, P. A. M. and de Leeuw, P. W. 2005. Cerebral hyperperfusion syndrome. *The Lancet Neurology* 4(12): 877-888.

Vansant, G., Pezzoli, P., Saiz, R., Birch, A., Duffy, C., Ferre, F. and Monforte, J. 2006. Gene expression analysis of troglitazone reveals its impact on multiple pathways in cell culture: a case for *in vitro* platforms combined with gene expression analysis for early (idiosyncratic) toxicity screening. *International Journal of Toxicology* 25: 85–94.

Varga, E. A., Sturm, A. C., Misita, C. P. and Moll, S. 2005. Homocysteine and MTHFR mutations: relation to thrombosis and coronary artery disease. *Circulation* 111: 289-293.

Vemuganti, R. and Dempsey, R. J. 2005. Carotid atherosclerotic plaques from symptomatic stroke patients share the molecular fingerprints to develop in a neoplastic fashion: a microarray analysis study. *Neuroscience* 131: 359–374.

Virmani, R., Burke, A. P., Farb, A. and Kolodgie, F. D. 2006. Pathology of the Vulnerable Plaque. *Journal of the American College of Cardiology* 47: 13-18.

Visse, R. and Nagase, H. 2003. Matrix metalloproteinases and tissue inhibitors of metalloproteinases : structure, function, and biochemistry. *Circulation Research* 92: 827-839.

Vos, P., Hogers, R., Bleeker, M., Reijans, M., van de Lee, T., Hornes, M., Frijters, A., Pot, J., Peleman, J., Kuiper, M. and Zabeau, M. 1995. AFLP: a new technique for DNA fingerprinting. *Nucleic Acids Research* 23(21): 4407-4414.

Wang, L., Ma, Y., Xie, X., Yang, Y., Fu, Z., Liu, F., Li, X., and Chen, B. 2011. Association of MMP-9 gene polymorphisms with acute coronary syndrome in the Uygur population of China. *World Journal of Emergency Medicine* 2(2): 104-110.

Wang, Q., Rao, S., Shen, G., Li, L., Moliterno, D. J., Newby, L. K., Rogers, W. J., Cannata, R., Zirzow, E., Elston, R. C. and Topol, E. J. 2004. Premature myocardial infarction novel susceptibility locus on chromosome 1p34-36 identified by genomewide linkage analysis. *American Journal of Human Genetics* 74: 262–271.

Wang, W., Lee, Y. and Lee, C. H. 2012. Review: The physiological and computational approaches for atherosclerosis treatment. *International Journal of Cardiology* 167(5): 1664-1676.

Wang, X. and Feuerstein, G. Z. 1997. The use of mRNA differential display for discovery of novel therapeutic targets in cardiovascular disease. *Cardiovascular Research* 35: 414–421.

Wang, X. L., Wang, J. and Wilcken, D. E. L. 1997. Interactive effect of the p53 gene and cigarette smoking on coronary artery disease. *Cardiovascular Research* 35: 250-255.

Wang, Y., Su, Y., Xu, Y., Pan, S. and Liu, G. 2010. Genetic polymorphism c.1562C>T of the MMP-9 is associated with macroangiopathy in type 2 diabetes mellitus. *Biochemical and Biophysical Research Communications* 391: 113–117.

Weiler, H. and Isermann, B. H. 2003. Thrombomodulin. *Journal of Thrombosis and Haemostasis* 1: 1515–24.

Werba, J. P., Martinez, V., Abulafia, D. P., Levy, R., Magarin˜os, G., Rey, R. H., Baetta, R., Soma, M. R., An˜el, A. D. and Cuniberti, L. A. 2001. Marked neointimal lipoprotein lipase increase in distinct models of proclivity to atherosclerosis: a feature independent of endothelial layer integrity. *Atherosclerosis* 156: 91–101.

Willer, C. J., Sanna, S., Jackson, A. U., Scuteri, A., Bonnycastle, L. L., Clarke, R., Heath, S. C., Timpson, N. J., Najjar, S. S., Stringham, H. M., Strait, J., Duren, W. L., Maschio, A., Busonero, F., Mulas, A., Albai, G., Swift, A. J., Morken, M. A., Narisu, N., Bennett, D., Parish, S., Shen, H., Galan, P., Meneton, P., Hercberg, S., Zelenika, D., Chen, W., Li, Y., Scott, L. J., Scheet, P. A., Sundvall, J., Watanabe, R. M., Nagaraja, R., Ebrahim, S., Lawlor, D. A., Ben-Shlomo, Y., Davey-Smith, G., Shuldiner, A. R., Collins, R., Bergman, R. N., Uda, M., Tuomilehto, J., Cao, A., Collins, F. S., Lakatta, E., Lathrop, G. M., Boehnke, M., Schlessinger, D., Mohlke, K. L. and Abecasis, G. R. 2008. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nature Genetics* 40(2): 161-169.

Wilson, P. W. F., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H. and Kannel, W. B. 1998. Prediction of coronary heart disease using risk factor categories. *Circulation* 97: 1837-1847.

Wilson, P. W., Schaefer, E. J., Larson, M. G. and Ordovas, J. M. 1996. Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 16: 1250-1255.

Wilson, T. A., Nicolosi, R. J., Lawton, C. W. and Babiak, J. 1999. Gender differences in response to a hypercholesterolemic diet in hamsters: effects on plasma lipoprotein cholesterol concentrations and early aortic atherosclerosis. *Atherosclerosis* 146: 83-91.

Windsor, L., Morahan, G., Huang, D., McCann, V., Jones, T., James, I., Christiansen, F. T. and Price, P. 2004. Alleles of the *IL12B* 3=UTR associate with late onset of type 1 diabetes. *Human Immunology* 65: 1432–1436.

Yadav, L. C. Y. K. 2007. Exercise in the management of coronary artery disease. *Medical Journal Armed Forces India* 63: 357-361.

Yakub, M., Moti, N., Parveen, S., Chaudhry, B., Azam, I., and Iqbal, M. P. 2012. Polymorphisms in MTHFR, MS and CBS genes and homocysteine levels in a Pakistani population. *PloS one* 7(3): e33222.

Yamamoto, M., Wakatsuki, T., Hada, A. and Ryo, A. 2001. Use of serial analysis of gene expression (SAGE) technology. *Journal of Immunological Methods* 250: 45-66.

Yang, H., Wang, H., Wang, J., Cai, Y., Gangqiao Zhou, G., He, F. and Qian, X. 2003. Multiplex single-nucleotide polymorphism genotyping by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Analytical Biochemistry* 314: 54-62.

Ye, S. Q. 2002. 6 Serial analysis of gene expression in human diseases. *Handbook of Immunohistochemistry and in Situ Hybridization of Human Carcinomas* 1: 85-98.

Youhanna, S., Platt, D. E., Rebeiz, A., Lauridsen, M., Deeb, M. E., Nasrallah, A., Alam, S., Puzantian, H., Kabbani, S., Ghoul, M., Zreik, T. G., Bayeha, H. E., Abchee, A. and Zalloua, P. 2010. Parental consanguinity and family history of coronary artery disease strongly predict early stenosis. *Atherosclerosis* 212: 559-563.

Yuan, A., Yu, C., Luh, K., Kuo, S., Lee, Y. and Yang, P. 2002. Aberrant p53 expression correlates with expression of vascular endothelial growth factor mRNA and interleukin-8 mRNA and neoangiogenesis in non–small-cell lung cancer. *Journal of Clinical Oncology* 20: 900-910.

Yusuf, S., Hawken, S., Ounpuu, S., Bautista, L., Franzosi, M. G., Commerford, P., Lang, C. C., Rumboldt, Z., Onen, C. L., Lisheng, L., Tanomsup, S., Wangai, P., Razak, F., Sharma, A. M. and Anand, S. S. 2005. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case—control study. *Lancet* 366: 1640-1649.

Zambahari, R. 2004. Trends in cardiovascular diseases and riskfactors in Malaysia. *International Congress Series* 1262: 446-449.

Zhang, B., Ye, S., Herrmann, S., Eriksson, P., de Maat, M., Evans, A., Arveiler, D., Luc, G., Cambien, F., Hamsten, A., Watkins, H. and Henney, A. M. 1999. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. *Circulation* 99: 1788-1794.

Zhang, K., Zhang, S., Zheng, K., Hou, Y., Liao, L., He, Y., Zhang, L., Nebert, D. W., Shi, J., Su, Z. and Xiao, C. 2004. *Biochemical and Biophysical Research Communications* 318: 4-10.

Zhang, K., Zhou, B., Wang, Y., Li Rao, L. and Zhang, L. 2012. The XRCC1 Arg280His polymorphism contributes to cancer susceptibility: an update by meta-analysis of 53 individual studies. *Gene* 510: 93–101.

Zhang, Z., Fu, G., Wang, M., Tong, N., Wang, S. and Zhang, Z. 2008. *P53* codon 72 polymorphism and ovarian cancer risk: a meta-analysis. *Journal of Nanjing Medical University* 22(5): 279-285.

Zhao, J., Zhou, X., Huang, J., Jianhong Chen, J. and Gu, D. 2005. Association study of the thrombomodulin _33GNA polymorphism with coronary artery disease and myocardial infarction in Chinese Han population. *International Journal of Cardiology* 100: 383-388.

Zhao, L. and Funk, C. D. 2004. Lipoxygenase pathways in atherosclerosis. *Trends Cardiovascular Medicine* 14: 191-195.

Zhi, H., Wang, H., Ren, L., Shi, Z., Peng, H., Cui, L., Ma, G., Ye, X., Feng, Y., Shen, C., Zhai, X., Zhang, C., Zen, K. and Liu, N. 2010. Functional polymorphisms of matrix metallopeptidase-9 and risk of coronary artery disease in a Chinese population. *Molecular Biology Reports* 37:13–20.

Zieske, A. W., McMahan, C. A., McGill Jr, H. C., Homma, S., Takei, H., Malcom, G. T., Tracy, R. E. and Strong, J. P. 2005. Smoking is associated with advanced coronary atherosclerosis in youth. *Atherosclerosis* 180: 87-92.

Zou, Z., Xu, X., Huang, X., Xiao, X., Ma, L., Sun, T., Dong, P., Wang, X. and Lin, X. 2011. High serum level of lutein may be protective against early atherosclerosis: The Beijing atherosclerosis study. *Atherosclerosis* 219: 789-793.