



UNIVERSITI PUTRA MALAYSIA

***EXPRESSION PROFILING OF DIABETIC AND HYPERTENSION-
ASSOCIATED GENES OF MALAYSIAN MALE SUBJECTS WITH
CORONARY HEART DISEASE IN A HOSPITAL IN MALAYSIA***

SALMA AHMADLOO

FPSK(P) 2018 28



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ASSOCIATED GENES OF MALAYSIAN MALE SUBJECTS WITH
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By
SALMA AHMADLOO

**Thesis Submitted to the School of Graduate Studies, Universiti
Putra Malaysia, in Fulfilment of the Requirements for the Degree
of Doctor of Philosophy**

November 2017



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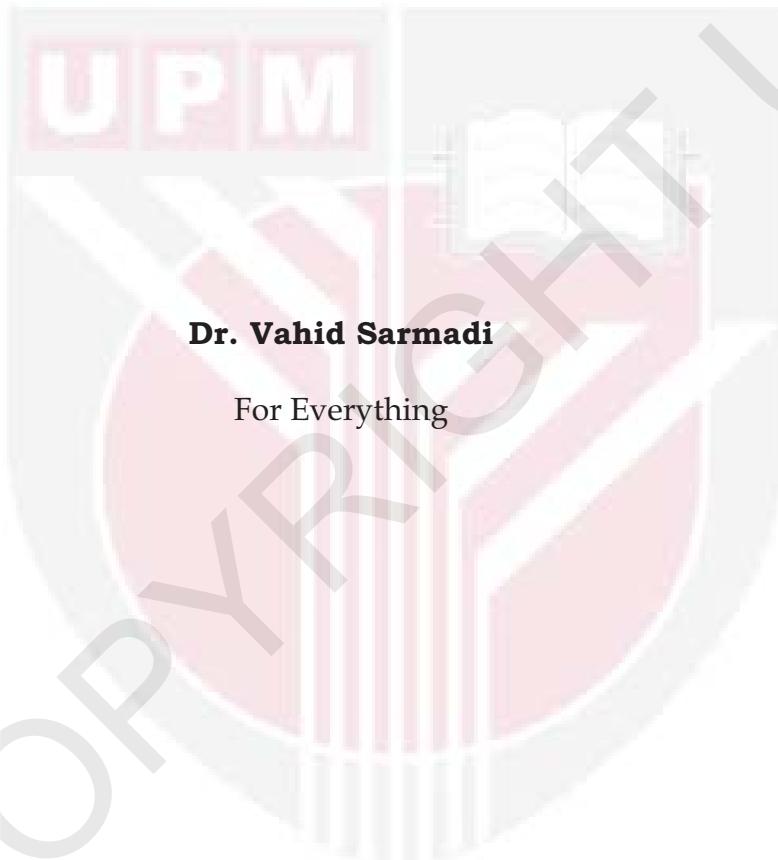
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DEDICATION

This thesis is dedicated to:



Abstract of thesis presented to the Senate of Universiti Putra Malaysia
in fulfilment of the requirement for the Degree of Doctor of Philosophy

**EXPRESSION PROFILING OF DIABETIC AND HYPERTENSION-
ASSOCIATED GENES OF MALAYSIAN MALE SUBJECTS WITH
CORONARY HEART DISEASE IN A HOSPITAL IN MALAYSIA**

By

SALMA AHMADLOO

November 2017

Chairman: Professor Patimah Ismail, PhD
Faculty: Medicine and Health Sciences

Coronary Heart Disease (CHD) is still the number-one killer in the world. As for Malaysia, the number of people with CHD has more than tripled in the past 40 years and the figures are still growing. Notably, many of the patients with CHD have at least one modifiable risk factor such as hypertension (HT) and diabetes mellitus (DM). HT and DM stand out as two major modifiable risk factors for CHD and it is well established that the incidence of over 80% of CHD is attributable to these two modifiable risk factors. This study was carried out for the purpose of profiling expression of DM and HT associated genes and identify related biological process and modulated signaling pathways of Malaysian male subjects with CHD from three ethnic group, namely Malay, Chinese and Indian.

In order to achieve the goal in group A, four groups of subjects were divided into: 1) 42 healthy subjects; 2) 42 subjects with only DM; 3) 42 subjects with only CHD, and 4) 42 subjects with CHD + DM. The RNA was extracted from blood specimens by mean of commercial extraction kits. The RT² Profiler™ PCR Array was utilized to determine gene profiling on group 1 and group 2, group 1 and group 3, group 1 and group 4. To validate the results of RT² profiler™ PCR Array, three of significantly dysregulated genes were selected and validation was conducted through Q-RT-PCR in a larger and independent population. For this purpose, new subjects were divided into: 1) 75 healthy subjects. 2) 75 subjects with DM+CHD. The Same pattern was followed in group B, DM replaced by HT in the groups with the same numbers,

to investigate and identify risk genes and modulated pathway/s related to HT which confer risk to CHD development. In order to validate the result in group B, single gene expression profiling was performed between 75 healthy individuals and 75 patients suffering from HT+CHD through Q-RT-PCR (An independent and larger population).

In group A, 12 significantly dysregulated genes related to diabetes and Toll-Like receptor signaling pathway were identified which may be a culprit to susceptible diabetic patients to CHD development. *In Silico* experiments imply a role for inflammatory responses in the circulating leukocytes as a biomarker reflecting initiation of CHD in patients with DM. In group B, 16 significantly dysregulated genes related to hypertension were identified and the RAAS cell signaling pathway was highlighted as a culprit in people suffering from hypertension which may be prone to CHD. *In Silico* analysis showed that the majority of the identified genes involved in renin-angiotensin regulation and other categories related to renin-angiotensin such as, regulation of blood volume and regulation of blood vessel by renin-angiotensin.

In conclusion, some differentially dysregulated genes and modulated pathways were identified which warrant further investigation in the setting of CHD and its risk factors. It is hoped that a greater understanding of genetic predisposition to CHD will unravel clues to its etiology and allow development of novel diagnostic and therapeutic tools to permit targeted interventions to reduce this global health burden.

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PROFIL EKSPRESI GEN DIKAITKAN DENGAN DIABETES DAN HIPERTENSI YANG BERKAITAN DENGAN SUBJEK LELAKI MALAYSIA DENGAN PENYAKIT JANTUNG KORONARI DI HOSPITAL

Oleh

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Penyakit jantung koronari atau “Coronary Heart Disease” (CHD) merupakan penyakit pembunuh nombor satu di dunia. Di Malaysia, bilangan pesakit CHD telah meningkat tiga kali ganda sejak 40 tahun yang lalu dan jumlahnya masih meningkat sehingga kini. Kebanyakan pesakit CHD mempunyai sekurang-kurangnya satu faktor risiko boleubah seperti Hipertensi (HT) dan Diabetes Mellitus (DM). Lebih daripada 80% insiden CHD dikaitkan dengan faktor bolehubah seperti DM dan HT. Kajian ini dijalankan bertujuan untuk melakukan profil pengekspresan DM dan HT berkaitan gen serta untuk mengenalpasti proses berkaitan biologi dan mengubah tapakjalan pengisyaratannya subjek lelaki warga Malaysia yang mempunyai CHD daripada tiga kumpulan etnik, iaitu Melayu, Cina dan India.

Bagi mencapai tujuan dalam kumpulan A, empat kumpulan subjek telah dibahagikan kepada: 1) 42 subjek sihat; 2) 42 subjek dengan DM sahaja; 3) 42 subjek dengan CHD sahaja, dan 4) 42 subjek dengan CHD + DM. RNA telah diekstrak keluar daripada spesimen darah menggunakan “commercial extraction kits.” *RT² Profiler™ PCR Array* telah digunakan bagi menentukan profil gen untuk kumpulan 1 dan kumpulan 2, kumpulan 1 dan kumpulan 3, kumpulan 1 dan kumpulan 4. Bagi mengesahkan keputusan *RT² Profiler™ PCR Array*, tiga gen yang signifikan telah dipilih dan pengesahan telah dijalankan melibatkan penggunaan Q-RT-PCR untuk populasi besar dan tak bersandar. Untuk tujuan ini, subjek baru telah dibahagikan kepada:

1) 75 subjek sihat, 2) 75 subjek dengan DM + CHD. Pesakit yang sama telah diikuti dalam kumpulan B, dimana DM digantikan dengan HT dalam kumpulan yang mempunyai sama bilangan, untuk menyelidik dan mengenalpasti gen risiko dan mengubah tapakjalan berkaitan kepada HT yang menyumbang kepada risiko perkembangan CHD. Bagi tujuan mengesahkan keputusan dalam kumpulan B, pengekspresan profil satu gen telah dijalankan diantara 75 individu sihat dan 75 pesakit yang menghidap HT + CHD menggunakan Q-RT-PCR (populasi besar dan tak bersandar).

Dalam kumpulan A, kami telah mengenalpasti 12 gen signifikan berkaitan penyakit Diabetes yang tidak normal serta laluan isyarat reseptor “Toll-Like” yang mungkin menjadi penyebab CHD di kalangan pesakit Diabetes. Eksperimen *in silico* menandakan peranan untuk tindakbalas inflamasi di dalam peredaran leukosit sebagai biopenanda yang melambangkan pencetus kepada CHD bagi pesakit DM. Dalam kumpulan B, 16 gen signifikan berkaitan penyakit Hypertensi yang tidak normal telah dikenalpasti. Laluan signal sel RAAS juga telah dikenalpasti dan ditekankan sebagai punca pendorong penyakit CHD di kalangan pesakit Hypertensi. Analisis *in silico* menunjukkan bahawa majoriti gen yang telah dikenalpasti terlibat dalam pengawalaturan renin-angiotensin dan kategori lain yang berkaitan kepada renin-angiotensin seperti kawalatur isipadu darah dan kawalatur salur darah oleh renin-angiotensin.

Kesimpulannya, kami telah mengenalpasti beberapa gen yang tidak normal dan laluan terubahsuai yang perlu dikaji dengan lebih mendalam kaitannya terhadap CHD serta faktor-faktor risikonya. Pemahaman yang lebih mendalam tentang faktor pendorong genetik dalam penyakit CHD diharapkan dapat mendedahkan lebih banyak petunjuk kepada punca penyakit tersebut. Selain itu, diharapkan agar alat-alat diagnostik serta rawatan terbaru dapat dihasilkan untuk melaksanakan langkah-langkah bagi mengurangkan beban kesihatan global ini.

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I certify that a Thesis Examination Committee has met on 8 November 2017 to conduct the final examination of Salma Ahmadloo on her thesis entitled "Expression Profiling of Diabetic and Hypertension-Associated Genes of Malaysian Male Subjects with Coronary Heart Disease in a Hospital in 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 Doctor of Philosophy.

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LIST OF ABBREVIATIONS

AER	Allelic Expression Ratio
ANRIL	Antisense Noncoding RNA in the INK4 Locus
Apoe	Apolipoprotein E
ARF	Alternative Reading Frame Transcript of CDKN2A
B2M	Beta-2-Microglobulin
BLAST	Basic Local Alignment Search Tool
BMI	Body Mass Index
Bp	Base Pairs
BP	Blood Pressure
BSA	Body Surface Area
CAD	Coronary Artery Disease
CCL18	Chemokine CC Motif Ligand 18
CCL2	Chemokine CC Motif Ligand 2
CDCV	Common Disease Common Variant
CDKN2A	Cyclin-Dependent Kinase 2A
CDKN2B	Cyclin-Dependent Kinase 2B
cDNA	Complementary Deoxyribonucleic Acid
CDRV	Common Disease Rare Variant
CHD	Coronary Heart Disease
CRP	C - Reactive Protein
Ct	Cycle Threshold for Real-Time PCR Analysis
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
EDTA	Ethylenediaminetetraacetic Acid
FLAP	5-Lipoxygenase Activating Protein
GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase
gDNA	Genomic DNA
GWA	Genome Wide Association
HT	Hypertension
HDL	High Density Lipoprotein
HDL	High Density Lipoprotein
HEK293	Human Embryonic Kidney 293 Cell Line
IHD	Ischemic Heart Disease
IL1RN	Interleukin 1 Receptor Antagonist
IL	Interleukin
LDLR	Low-Density-Lipoprotein Receptor
LV	Left Ventricle
LVIDD	Left Ventricular Internal Diameter Diastole
LVIDS	Left Ventricular Internal Diameter Systole
MI	Myocardial Infarction
MIQE	Minimum Information for Publication of Quantitative Real-Time PCR Experiments
MLH1	MutL Homolog 1
MLPA	Multiplex Ligation-Dependent Probe Amplification
NCBI	National Center for Biotechnology Information

OR	Odds Ratio
OxLDL	Oxidized LDL
PCR	Polymerase Chain Reaction
RE	Restriction Enzyme
RNA	Ribonucleic Acid
RPM	Revolutions per Minute
RT	Reverse Transcription
SAP	Shrimp Alkaline Phosphatase
SMC	Smooth Muscle Cell
SNP	Single Nucleotide Polymorphism
T2 DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
TLR4	Toll-like Receptor 4
WGA	Whole Genome Amplification
WHR	Waist-Hip Ratio
WTCCC	Welcome Trust Case Control Consortium



CHAPTER 1

INTRODUCTION

1.1 Background

Coronary heart disease (CHD) encompasses a spectrum of clinical diagnoses such as myocardial infarction (MI) and angina that are induced by coronary atherosclerosis, a pervasive degenerative disease in which plaques (fibrous matrix and lipid) are built up in the wall of arterial vessel (Fishbein and Fishbein, 2015; Xu *et al.*, 2015). Rupture of unstable plaques in coronary arteries causes a critical condition with high mortality through releasing of the thrombogenic material into the lumen of the vessel leading to vessel occlusion, coronary thrombosis, and subsequent infarction of the myocardium (Hansson, 2005; Watkins and Farrall, 2006; Montalescot *et al.*, 2013). CHD is globally considered a main cause of death in both developed and developing countries (Hadaegh *et al.*, 2009; Pagidipati and Gaziano, 2013). According to the statistics issued by the World Health Organization (WHO), 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to CHD (WHO, 2016a).

As for Malaysia, the number of people with CHD has more than tripled in the past 40 years and the figures are still growing (Ang and Chan, 2016; WHO, 2016c). Most CHD are thought to have a multifactorial Genetic basis, involving genetic and environmental factors in interaction that determine the susceptibility of a person to the disease (Okrainec *et al.*, 2004; Libby and Theroux, 2005; Ross, 2016). The term ‘risk factors’ is generally used to describe those characteristics found in an individual who have been shown in various studies, related to subsequent occurrence of CHD (Yeolekar, 2003; WHO, 2009). Notably, many of the patients with CHD have multiple risk factors, including non-modifiable (such as age and gender) and modifiable risk factor (such as hypertension and diabetes mellitus) (Baker *et al.*, 2007; Roger *et al.*, 2012b; Dawber *et al.*, 2015). Diabetes mellitus (Arch and Korytkowski, 1999; Yeboah *et al.*, 2014) and hypertension (Franklin *et al.*, 2001; Santulli, 2012) stand out as two major modifiable risk factors for CHD.

Although around 80% of CHD cases are attributable to the major modifiable risk factors, on the other hand, the differences seen between the ethnic groups could be due to genetic predisposition (Muda *et al.*,

2013a). Corresponded by many studies on CHD and its genetic background which have identified a number of genes related to CHD pathogenesis (Ashburner *et al.*, 2000; Arnett *et al.*, 2007; Willer *et al.*, 2008; McPherson and Tybjaerg-Hansen, 2016). Gender is another important risk factor in incidence of CHD and many studies have noted difference between male and female in CHD distribution among populations (Emslie, 2005; Maas and Appelman, 2010; Sharma and Gulati, 2013). Now it is well established that CHD are significantly more prevalent in male gender (Reikvam and Hagen, 2002; Maas and Appelman, 2010) due to the fact that the risk factors are more prevalent in male compared to female patients. Given that CHD is increasing at an alarming rate in Malaysian male and the major risk factors are strong predictors of an increased likelihood for CHD (Broadbent *et al.*, 2008; Kraja *et al.*, 2011; Mangiapane, 2013; Sadeghi *et al.*, 2013; Bittencourt *et al.*, 2014), there is paucity of data regarding the mechanism of the major risk factors and CHD development. Thus, there is an urgent need to determine the association between genes related to the major risk factors and Malaysian male subjects with CHD.

1.2 Problem statement

Ischaemic heart disease has remained the principal cause of death among Malaysians over the past 10 years, recording 13.5 per cent in 2016, based on the findings of the Statistics Department (MALAYSIA, 2016). According to the WHO, CHD in terms of health-related problems and diseases is the number one killer in Malaysia (WHO, 2015). While in the past decades, normally, CHD were found in the old populations, nowadays it is often encountered by young adults and around 4-10% of people with documented CHD are less than 55 years old (Thompson, 2002; De Sutter *et al.*, 2003; Mohammad *et al.*, 2015) and necessarily, patients belonging to a particular subgroup, early age CHD, because of devastating effect on individuals, families and the society, need much more attention. In some countries studies on CHD may be relevant to the populations studied, but in Malaysia the data on CHD is rare.

Besides, the rising burden of major risk factors such as diabetes and hypertension which have emerged as major medical and public health issues worldwide (Pradeepa, 2013), is more alarming (Goswami *et al.*, 2016). For example, according to WHO, the number of diabetic patients has nearly quadrupled within almost three decades (108 million in 1980 vs. 422 million in 2014) (WHO, 2016a) and based on the new study, conducted by scientists at Imperial College London, the number of people with hypertension has nearly doubled in 40 years

(Collaboration, 2017). Hence, identifying the genes and involved signaling pathways related to the modifiable risk factors which are major contributor to CHD events is of high priority.

1.3 Significance of study

Despite being known as the number-one killer in the world, clinical trials have shown the CHD to be a preventable disease, and by treating known risk factors the morbidity and mortality can be diminished by at least 30% to 40% (Allender *et al.*, 2007; McGill Jr, 2010; Smith Jr *et al.*, 2011). On the other hand, around 50% of predisposition is claimed to be linked to genetic susceptibility (Sing and Moll, 1990; Lusis *et al.*, 2004; Roberts, 2015). As claimed by some researchers, in order to tackle the challenge of preventing CHD in the present century, it is essential to have more comprehensive data regarding the association of genetic risk factors in this disease. Despite the findings of the recent studies that have indicated the role of multiple genetic factors each with modest effects in the development of CHD (Galton, 1988; Wang, 2005; Watkins and Farrall, 2006; Visel *et al.*, 2010; Ozaki and Tanaka, 2016), the genes and respective molecular pathway/s involved in CHD still remain poorly understood. This study attempts to determine genetic contribution and patterns of altered gene expression related to the major risk factors of CHD, as well as to identify novel molecular signaling pathway/s to capture groups of genes with the highest likelihood of increasing CHD risk and introducing as biomarker/s for prognosis of CHD.

1.4 Objectives of the study

1.4.1 General objective

To determine the expression profiling of diabetic and hypertension associated genes of Malaysian male subjects with coronary heart disease.

1.4.2 Specific objectives

- 1) To investigate gene expression profiling of DM risk genes on diabetic patients VS Malaysian healthy people.
- 2) To determine whether DM related genes confer risk to CHD pathogenesis.

- 3) To investigate gene expression profiling of HT risk genes on hypertensive cases and healthy people.
- 4) To determine whether hypertension related genes confer risk to CHD pathogenesis.
- 5) To identify signaling pathway/s implicated in CHD pathogenesis by conduction Insilco analysis in group A & B.
- 6) To validate PCR Array results of group A & B through single gene expression analysis by quantitative RT-PCR.



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