UNIVERSITI PUTRA MALAYSIA

EXPRESSION ANALYSIS OF COMMD5, NPPA, SLC7A1 AND AT1R GENES AMONG HYPERTENSIVE MALAYS

BAN WAHEED HUSSEIN BDAIR

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By

BAN WAHEED HUSSEIN BDAIR

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

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DEDICATION

I dedicate the thesis to the people who without them I won't have reached where I am today

My soul husband

My beloved sons and daughters

My dear father

My caring mother

My supportive brother and sister

All lovely lecturer, teachers and friends

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

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Chairman : Professor Patimah Ismail, PhD
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Hypertension is one of the most common and known risk factors for cardiovascular disease. This disease affects structures and functions of small muscles arteries, arterioles and other blood vessels. It is known to cause varying damages in different organs like brain, eye and kidney which may eventually lead to stroke, poor vision and renal disease. By 2025, it has been predicted that about 1.56 billion people are expected to have high blood pressure. Recently, Global Burden of Disease reported high-level blood pressure as the most significant risk factor for mortality. In the year 2011, National Health Morbidity Survey (NHMS) IV reported 32.7% as the prevalence rate of hypertension in Malaysia. Environmental risk factors such as sedentary lifestyle, dietary factors, smoking, and lack of physical activity in combination with genetic factors play important role in progression of hypertension.

Of recent, human genetic studies have reported several candidate genes such as COMMD5 (COMM Domain-Containing Protein 5), which relates with calcium haemostasis and NPPA (Natriuretic Peptide A), a gene that play key roles in maintenance of cardiovascular homeostasis as well as vasodilation. Similarly, the SLC7A1 (solute carrier family 7 member 1) gene which is involved in the transport of the cationic amino acids (arginine) and AT1R (Angiotensin II Receptor Type 1) that controls blood pressure/ volume in the cardiovascular system are also potent candidate genes. Although the functions of these genes have been identified, there is absence of detailed comprehensive analysis of the expression of these genes collectively in association with hypertension among Malays. In line with this, the present study aimed at determining the expression level of these genes (COMMD5, NPPA, SLC7A1, and AT1R) among hypertensive Malay subjects. Therefore, a total of 100 newly diagnosed hypertensive patients and 100 unrelated healthy individuals were recruited. Total RNA was extracted from whole blood specimen using RNA extraction kit and the target genes were quantitated using Real Time Quantitative Polymerase Chain Reaction (RT-

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qPCR). General Linear Model analysis was performed using SPSS software and $p \leq 0.05$ was deemed significant and analysis of gene expression and relative expression in qPCR was performed using REST software. The demographic characteristic of the subject such as body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), low density lipoprotein (LDL), triglyceride (TG) and cholesterol (Chol) were shown to be differently significant ($p<0.05$) in experimental subjects compared to control. Moreover, age and high density lipoprotein (HDL) did not show any significance ($p>0.05$). Gene expression pattern was determined in hypertensive patients and compared with control. COMMD5 and AT1R genes were significantly upregulated in hypertensive patients compared with control ($p<0.05$), while SLC7A1 and NPPA genes were downregulated in hypertensive patients compared with healthy individuals. This study demonstrated that COMMD5, NPPA, SLC7A1, and AT1R might be involved in pathogenesis of hypertension, and hence could be used as diagnostic biomarkers in the prediction of hypertension in Malay subjects.

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

ANALISIS EXPRESI *COMMD5, NPPA, SLC7A1,* DAN *AT1R* GENESIS DENGAN SUBJEK BAHARU HIPERTENSIF

Oleh

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Pengerusi : Profesor Patimah Ismail, PhD
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Hipertensi adalah salah satu faktor risiko yang paling dikenali dan boleh dirawat untuk penyakit kardiovaskular. Hipertensi memberi kesan kepada struktur dan fungsi arteri otot kecil, arteriol dan saluran darah yang lain. Ia diketahui menyebabkan kerosakan pada kadar berubah-ubah dalam organ-organ yang berbeza seperti; Buah pinggang, otak dan mata yang boleh membawa kepada penyakit buah pinggang yang akhirnya menyebabkan strok. Menjelang 2025, diharapkan bahawa 1.56 bilion orang akan mengalami hipertensi. Satu laporan baru-baru ini mengenai Kajian Beban Penyakit Global, BP peringkat tinggi sebagai faktor risiko yang paling penting untuk kematian. Menurut Kajian Kesihatan Morbiditi Nasional (NHMS) IV, prevalensi hipertensi di Malaysia adalah 32.7% pada tahun 2011. Faktor risiko alam sekitar seperti gaya hidup tidak aktif, faktor pemakanan, merokok, dan kurangnya aktiviti fizikal dalam kombinasi dengan faktor genetik memainkan peranan penting dalam Perkembangan hipertensi.

Baru-baru ini, kajian genetik manusia telah melaporkan beberapa gen calon seperti COMMD5 (COMM Domain-Containing Protein 5) yang berkaitan dengan haemostasis kalsium, NPPA (Natriuretic Peptide A) yang memainkan peranan penting dalam homeostasis kardiovaskular melalui peraturan natriuresis, diuresis, dan vasodilation . SLC7A1 (keluarga pembawa larut 7 anggota 1) yang terlibat dalam pengangkutan asid amino kationik (arginine) dan AT1R (Angiotensin II Receptor Type 1) yang berfungsi sebagai alat pengukur penting yang mengawal tekanan darah dan volum dalam sistem kardiovaskular. Tujuan kajian ini adalah untuk menentukan corak ekspresi gen ini (COMMD5, NPPA, SLC7A1, dan AT1R) di kalangan subjek Bahasa Melayu hipertensi. Sebanyak 100 pesakit hipertensi yang baru didiagnosis dan 100 orang yang tidak sihat yang sihat yang semuanya menjalani angiografi telah direkrut. Jumlah RNA diekstrak daripada spesimen darah keseluruhan menggunakan kit pengekstrakan. QPCR digunakan untuk menguatkan salinan cDNA sasaran RNA

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yang diekstrak. Sensitif dan serba boleh, qPCR digunakan untuk mengambil dan mengklonkan terma mRNA 5 'dan 3' dan menghasilkan pustaka cDNA yang besar dari sejumlah kecil mRNA. Analisa model Linear Umum dilakukan menggunakan perisian SPSS dan $p \leq 0.05$ dianggap penting dan analisis ekspresi gen dan ekspresi relatif dalam qPCR dilakukan menggunakan perisian REST. Ciri demografi subjek seperti indeks jisim badan (BMI), tekanan darah sistolik (SBP), tekanan darah diastolik (DBP), lipoprotein ketumpatan rendah (LDL), trigliserida (TG) dan kolesterol (Chol) Ketara ($p < 0.05$) dalam mata pelajaran eksperimen berbanding kawalan. Lebih-lebih lagi, umur dan lipoprotein ketumpatan tinggi (HDL) tidak menunjukkan sebarang kepentingan ($p > 0.05$). Corak ungkapan gen ditentukan dalam pesakit hipertensi dan dibandingkan dengan kawalan. GenSR dan gen AT1R telah dikawal dengan ketara dalam pesakit hipertensi berbanding dengan kawalan ($p < 0.05$), manakala gen SLC7A1 dan NPPA dikurangkan dalam pesakit hipertensi berbanding pesakit yang sihat. Kajian ini menunjukkan bahawa COMMD5, NPPA, SLC7A1, dan AT1R mungkin terlibat dalam patogenesis hipertensi, dan dengan itu boleh digunakan sebagai biomarker diagnostik dalam ramalan hipertensi dalam mata pelajaran Melayu.

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

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Declaration by graduate student

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
Ang I	angiotensin I
Ang II	angiotensin II
ANOVA	Analyze of Variance
AT1R	Angiotensin II Receptor Type 1
AT2R	angiotensin II type 2 receptor
BMI	body mass index
BP	Blood pressure
CAT-1	Cationic Amino Acid Transporter 1
CD	cardiovascular disease
cDNA	Complementary Deoxyribonucleic acid
Chol	cholesterol
CI	confidence interval
COMMD5	COMM Domain-Containing Protein 5
CT	Cycle Threshold for Real- Time PCR analysis
CVD	Cardiovascular Disease
DBP	diastolic blood pressure
EH	Essential hypertension
GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase
GWAS	Genome -Wide Association Studies
HbA1c	Glycated Haemoglobin
HCaRG	hypertension-related, calcium-regulated gene
HDL	high density lipoprotein
Kg	Kilogram
LDL	low density lipoprotein
ml	milliliter
mm Hg	millimetre of mercury
ng	Nano gram
NHMS	National Health Morbidity Survey
NMRR	National Medical Research Register

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NPPA	Natriuretic Peptide A
NTC	No Template Control
OD	optical densities
qPCR	quantitative Polymerase Chain Reaction
RAAS	renin-angiotensin-aldosterone system
REST	Relative Expression Software Tool
RIN	RNA Integrity Number
RNA	Ribonucleic Acid
S1	Stage 1 hypertension
S2	Stage 2 hypertension
SBP	systolic blood pressure
SLC7A1	solute carrier family 7 member 1
SNP	Single Nucleotide Polymorphism
SPSS	statistical package for social sciences
TG	triglyceride
UV	Ultraviolet
WHO	World Health Organization

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CHAPTER 1

INTRODUCTION

1.1 Background of the study

Hypertension or increase in blood pressure (BP) is a major risk factor for cardiovascular diseases (CVD). Hypertension have been reported to affect over one billion people worldwide (Kearney *et al*., 2005) , leading to heart attacks and strokes. It has also been estimated that increase in blood pressure currently kills 9 million people every year (WHO, 2013). Hypertension is diagnosed from the force of arterial heartbeat-induced blood pressure. In normal individuals, the blood pressure is usually 120/80mmHg which implies a systolic blood pressure of 120 mmHg and a diastolic pressure of 80 mmHg. Blood pressures ≤130/89 mmHg are considered to exceed the normal ranged and are termed as pre-hypertension. Hypertension however is characterised by a blood pressure ≥140/80 mmHg (Glasser *et al*., 2013; Weber *et al*., 2014). Two broad categories are employed for the classification of hypertension, these are as Essential Hypertension (EH) or Secondary Hypertension (SE). About 95% of hypertensive cases are EH and its diagnosed when there is no evidence of high blood pressure susceptibility to medical conditions (Go *et al*., 2013). However, SE constitutes a small number of cases and is associated with diseases such as Cushing's syndrome, chronic renal failure or Conn's syndrome (Schaefer and Mehls, 2004; Ceccato and Boscaro, 2016) .

Many factors contribute to the presence of high blood pressure, these factors include lifestyle, genetic factors, eating habits and other medical complications (Niiranen *et al*., 2017). Elevated BP has been associated with obesity, smoking, less physical activity, too much alcohol consumption and high salt intake (Carretero and Oparil, 2000; Weber *et al*., 2014) While the role of environment is known to impact on the BP, genetic factors can not be ignored as it may form the underlying basis of this condition. A complex form of genetic traits resulting from multiple genes being controlled by interactions between one gene and another as well as between a gene and its environment is widely referred to as polygenic mutation and this have been shown to be the primary culprit in EH (Chern and Chiang, 2004; Singh *et al*., 2016).

It has been suggested that hypertension has a basis in genetics as interactions between genes and external factors as well as within genes have led to diabetes in already susceptible individuals (Williams *et al*., 1991; Chandra *et al*., 2015). In an effort to maintain physiological homeostasis, a specific genetic system interacts with candidate genes to regulate blood pressure. Renin angiotensin aldosterone system (RAAS) and in association with candidate genes. Atrial natriuretic peptide (*NPPA*) and Angiotensin-II Type-1 Receptor (*AT1R*) are RAAS mediators with significant roles in hypertension through regulation of aldosterone secretion and cardio renal homeostasis, respectively. Endothelium dysfunction leading to hypertension could result from variations in the *SLC7A1* gene as reported by genetic studies.

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Recently, the Qiagen Company indicated how *COMMD5* gene is involved and associated with hypertension (Matsuda *et al.*, 2014). *COMMD5* was previously known as HCaRG, first identified in spontaneously hypertensive rats (SHR) (Solban *et al*., 2001). Gene expression is the most basic level in which the genotype of an organism causes the phenotype. A good way to consider gene expression is to interpret the information stored in the cell DNA as a mediator to produce a phenotypic output by gene transcription and mRNA progression. The ultimate effect on the phenotype is primarily through the synthesis of proteins, some of which structurally control the shape and characteristics of an organism, while others may be enzymes responsible for catalyzing specific metabolic pathways (Morley *et al*., 2004). Therefore, the present study focused on the gene expression levels of key genes (*AT1R*, *NPPA*, *SLC7A1* and *COMMD5*) associated with hypertension amongst Malays. It is important to state however, that this study ensured that the respondents are three-generational genetic hierarchical Malays with no Chinese, Indian or other race within the generations. This will eliminate to a high extent, the effect of genetic variations that may arise as a result of inter-racial marriages.

1.2 Problem statement

In developed and developing countries, hypertension has been identified as a serious threat to public health. It is one of the risk factors for cardiovascular death (Kishore *et al.*, 2016). Globally, cardiovascular disease cause for about 17 million deaths a year (WHO, 2013). Hypertensive complications are reported in the world every year with 9.4 million deaths (Lim *et al*., 2012). Hypertension causes heart disease that lead to at least 45% dead while 51% die due to stroke deaths (WHO, 2013).

There were 1.33 billion people living with high BP in the year 2015, and most of them in middle income and low income countries. Females aged 18 years and older have around 20% prevalence of high BP while the prevalence in males is around 24% (Collaboration, 2016). In Malaysia, the National Health Morbidity Survey (NHMS) IV conducted in 2011, reported 43.5% as the prevalence rate of hypertension in adults ≥30years (Naing *et al*., 2016), which implies a continuous increase in the prevalence level when compared to 32.9% reported in NHMS II 1996 (Lim and Morad, 2004) and 42.6 % reported in NHMS III 2006 (Nor *et al*., 2008) . Another study conducted in 2016, highlights the shocking situation, almost half of adults older than 30 years old suffered from high BP. Overall, the hypertension prevalence was 47.9 % and was higher in men (43.5 %) than women (41.0 %) (Abdul-Razak *et al*., 2016).

Genetics plays a major role in hypertension development and progression as many studies are currently focusing on gene therapy in the treatment of metabolic and cardiovascular disorders (Padmanabhan *et al*., 2015). Additionally, there is a gap in the availability of research materials collectively associating *AT1R*, *NPPA*, *SLC7A1* and *COMMD5* genes with hypertension especially among Malays. This is a novel study on the gene expression of *NPPA*, *SLC7A1* and *COMMD5* in association with hypertension among Malays. Hence, this is the first study to particularly identify these genes among hypertensive Malay ethnic group in Malaysian population.

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1.3 Significance of the study

The Cross sectional study attempt to determine the presence of variation within candidate genes (*AT1R*, *NPPA*, *SLC7A1* and *COMMD5*) which might be associated with the pathogenesis of hypertension among hypertensive Malay as compared to non-hypertensive Malays. Analysis of these genes provides better approach for identifying the level of expression and their possible correlation with the disease. The physicians can recognize the onset of hypertension in high risk individuals which can be prevented or delayed. Results of this study will be compared with other studies worldwide and would form a deposit database that could be used for Malaysian genetic database for future references.

1.4 Hypothesis

There is an association between *AT1R*, *NPPA*, *SLC7A1* and *COMMD5* genes expression among hypertensive subjects.

1.5 General objective

To identify the expression levels of *AT1R*, *NPPA*, *SLC7A1* and *COMMD5* genes and analyse their association with the severity of hypertension amongst Malay subjects.

1.6 Specific objectives

1. To correlate the demographic, physical and cardiological description of respondents with their hypertensive condition.
2. To determine the expression levels of *AT1R*, *NPPA*, *SLC7A1* and *COMMD5* genes in patients with hypertension and compare with non-hypertensive subjects.
3. To evaluate the relationship between the expression levels of *AT1R*, *NPPA*, *SLC7A1* and *COMMD5* genes and severity of hypertension.
4. To identify changes in some biochemical indices and associate these changes with gene expression in the hypertensive patients.

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