UNIVERSITI PUTRA MALAYSIA

GENETIC ANALYSIS OF BETA 2 ADRENERGIC AND DOPAMINE RECEPTOR GENE POLYMORPHISMS IN HYPERTENSIVE SUBJECTS AT HOSPITAL SEREMBAN, MALAYSIA

MAKANKO KOMARA

FPSK(m) 2013 58

GENETIC ANALYSIS OF BETA 2 ADRENERGIC AND DOPAMINE RECEPTOR GENE POLYMORPHISMS IN HYPERTENSIVE SUBJECTS AT HOSPITAL SEREMBAN, MALAYSIA

MAKANKO KOMARA

MASTER OF SCIENCE
UNIVERSITI PUTRA MALAYSIA

2013

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

GENETIC ANALYSIS OF BETA 2 ADRENERGIC AND DOPAMINE RECEPTOR GENE POLYMORPHISMS HYPERTENSIVE SUBJECTS AT HOSPITAL SEREMBAN, MALAYSIA

By

MAKANKO KOMARA

January 2013

Chairman: **Professor. Patimah Ismail, PhD**

Faculty: **Medicine and Health Sciences**

Essential hypertension which is a major risk factor for cardiovascular diseases is a complex trait influenced by multiple genes and environmental factors. According to The Third National Health and Morbidity Survey in 2008, the prevalence of hypertension among Malaysian adults was 43%. The heritability of hypertension has been estimated to be 60%. β2 adrenoceptor and Dopamine receptor genes have been known to play a major role in blood pressure regulation. This study aims to determine the association of Arg16Gly (rs1042713), Gln27Glu (rs1042714) and Thr164Ile (rs1800888) polymorphisms of β2 adrenoceptor and A-48G (rs4532) and *Taq*1A (rs1800497) polymorphism of dopamine receptor in Malaysian hypertensive subjects. A total of 160 of each cases and control subjects were recruited. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and anthropometric measurement were obtained from each subject. Biochemical analysis of lipid profile

was measured using auto analyzer. DNA samples were extracted from blood and buccal cells. Genotyping was done by PCR-Restriction Fragment length Polymorphism. SBP, DBP, BMI and biochemical analysis were significantly different between cases and controls ($p<0.05$). Genotypes of Arg16Arg, Arg16Gly and Gly16Gly among cases were 22.5%, 70% and 7.5% respectively compared to 33.1%, 63.1% and 3.8% respectively among controls. The genotype frequencies of Gln27Gln, Gln27Glu and Glu27Glu among cases were 41.1%, 50% and 1.9% respectively compared to 77.5%, 20.6% and 1.9% respectively among controls. For Thr164Ile polymorphism, all subjects were homozygote for the wild type genotype. For the Dopamine receptor 1 gene polymorphism, the genotypes frequencies of AA, AG and GG among cases were 54.4%, 38.8% and 6.9% respectively, while the frequencies were 61.2%, 32.5% and 6.2% among control subjects. The genotype frequencies of A1A1, A1A2 and A2A2 of Dopamine receptor 2 gene among cases were 16.2%, 61.9% and 21.95 respectively compared to 14.4%, 50.6% and 35% respectively among control subjects. In this study two polymorphisms were significantly associate with hypertension; Gln27Glu and *Taq*1A polymorphisms (p = 0.000) and (p= 0.033). In ANOVA analysis, the Age, BMI, SBP, DBP and biochemical analysis results were not significantly associated with study genotypes. The analysis of Multifactor dimensionality reduction showed a significant interaction between β2 adrenoceptor and dopamine receptor genes polymorphism (p=0.001). This study suggests that Gln27Glu and *Taq*1A polymorphism of β2 adrenoceptor and dopamine receptor genes could be a risk factor associated with hypertension among Malaysians with possible interaction between the genotypes of both genes.

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

ANALISIS GENETIK ADRENERGIC BETA2 DAN POLIMORFISME GEN RESEPTOR DOPAMIN DALAM SUBJEK HIPERTENSI DI HOSPITAL SEREMBAN, MALAYSIA

Oleh

MAKANKO KOMARA

Pengerusi : Professor. Patimah Ismail, PhD

Fakulti : Perubatan Dan Sains Kesihatan

Hipertensi esensial yang merupakan faktor risiko utama untuk penyakit kardiovaskular, adalah ciri kompleks trait dipengaruhi oleh pelbagai gen dan faktor persekitaran. Menurut Kajian Kesihatan dan Morbiditi Negara Ketiga (NHMS III) pada tahun 2008, kadar prevalen hipertensi di kalangan orang dewasa Malaysia ialah 43%. Sebanyak 60% telah dianggarkan bahawa hipertensi diwariskan kepada generasi seterusnya. Gen reseptor B2 adrenoceptor dan gen reseptor Dopamine telah dikenal pasti memainkan peranan utama dalam pengawalaturan tekanan darah. Kajian ini bertujuan untuk menetukan perkaitan polimorfisme β2 adrenoceptor Arg16Gly (rs1042713), Gln27Glu (rs1042714) dan Thr164Ile (rs1800888) serta polimorfisme reseptor dopamine A-48G (rs4532) dan Taq1A (rs1800497) dalam subjek hipertensi di Malaysia. Sebanyak 160 orang bagi setiap subjek kes dan kawalan, telah direkrut. Tekanan darah sistolik (SBP), tekanan darah diastolik (DBP) dan pengukuran antropometri telah diperolehi daripada setiap subjek. Analisis biokimia profil lipid telah dilakukan menggunakan penganalisis automatik. Sampel DNA telah diekstrak daripada darah dan sel bukal. Genotyping telah dilakukan dengan teknik Tindak Balas Rantaian Polimerase - Polimorfisme Panjang Cebisan

Pemotongan (PCR-RFLP). SBP, DBP, BMI dan analisis biokimia mempunyai perbezaan yang signifikan antara kes dan kawalan ($p < 0.05$). Genotip Arg16Arg, Arg16Gly dan Gly16Gly di kalangan kes dengan masing-masing adalah 22.5%, 70% dan 7.5% berbanding dengan 33.1%, 63.1% dan 3.8% di kalangan kawalan. Frekuensi genotip Gln27Gln, Gln27Glu dan Glu27Glu di kalangan kes-kes adalah 41.1%, 50% dan 1.9% berbanding dengan 77.5%, 20.6% dan 1.9% masing-masing di kalangan kawalan. Bagi polymorfisme Thr164Ile, semua subjek adalah homozigot untuk genotip jenis liar. Bagi polymorfisme DRD1 gen, frekuensi genotip AA, AG dan GG di kalangan kes masing-masing adalah 54.4%, 38.8% dan 6.9%, manakala frekuensi 61.2%, 32.5% dan 6.2% di kalangan subjek kawalan. Frekuensi genotip A1A1, A1A2 dan A2A2-DRD2 kalangan kes masing-masing adalah 16.2%, 61.9% dan 21.95 berbanding 14.4%, 50.6% dan 35% masing-masing di kalangan subjek kawalan. Dalam kajian ini dua polimorfisme iaitu polimorfisme Gln27Glu dan Taq1A, mempunyai signifikasi yang ketara dengan hipertensi dengan nilai $p = 0.000$ dan 0.033. Umur, BMI, SBP, DBP dan keputusan analisis biokimia adalah tidak signifikan berbanding kajian genotip. Analisis pelbagai faktor pengurangan dimensi menunjukkan interaksi yang signifikan antara β2 adrenoceptor dan polymorfisme gen reseptor dopamin ($p < 0.001$). Kajian ini menunjukkan bahawa polymorfisme Gln27Glu dan Taq1A β2 gen reseptor adrenoceptor dan dopamine boleh menjadi faktor risiko yang dikaitkan dengan tekanan darah tinggi di kalangan rakyat Malaysia dengan kemungkinan interaksi antara genotip kedua-dua gen.

ACKNOWLEDGEMENTS

First and foremost I would like to thank Almighty Allah subahanahu wataala for His blessings and mercy that made this research and work possible. I would like to thank my mother, my siblings and my husband for their moral support.

I am very thankful to my supervisor Professor. Dr. Patimah Ismail, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, for her valuable advice and support. I am also thankful to my cosupervisor Dr. Suhaili Abu Bakar for continuous guidance and encouragement. My appreciation also goes to Dr. R.Vasudevan who did not hesitate in providing the help and support and share his experience with us. I am also thankful to all the staff and students of Molecular biology and bioinformatics laboratory UPM.

Finally, great thanks goes to Mr. Mohammed Jokha, and all staff of venipucture unit of hospital Seremban for their role in providing the help and support during my sample collection.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADRB2	β2 adrenoceptor gene
Arg	Arginine
BMI	Body Mass Index
bp	Base Pair
cAMP	Cyclic Adenosine Monophosphate
CPG	Clinical Practice Guindeline
CVC	Cross Validation Consistency
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic acid
DRD1	Dopamine receptor 1 gene
DRD2	Dopamine receptor 2 gene
Gln	Glutamine
Glu	Glutamic acid
GWAS	Genome Wide Association Studies
HDL	High Density Lipoprotein
Ile	Isoleucine
JNC-6	The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC-7	The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL	Low Density Lipoprotein
mmHg	millimeter mercury
Na-H	Sodium /Hydrogen exchanger
Na-K	Sodium/Potassium exchanger
NCBI	National Center for Biotechnology Information
nm	nanometer
PCR-RFLP	Polymerase Chain Reaction Restriction Fragments Length Polymorphism
SBP	Systolic Blood Pressure
SNP	Single Nucleotide Polymorphism
TG	Triglyceride
Thr	Threonine
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

CHAPTER I

INTRODUCTION

Background of the Study

High blood Pressure or hypertension is defined as sustained increase of systolic blood pressure of 140 millimeter mercury (mmHg) or greater and/or diastolic blood pressure of 90 mmHg or greater. Hypertension is a major public health problem and the leading cause of death worldwide (Chockalingam, 2008). Moreover, hypertension is known as a risk factor for cardiovascular and renal diseases. It has been estimated that 82% to 95% of all hypertension cases are primary or essential hypertension with no specific cause (Carey, 2008). Secondary form of hypertension is caused by some medical conditions such as, renovascular disease, Cushing Syndrome and primary aldosteronism (Carey, 2008).

Hypertension is a complex disease controlled by multiple genes and environmental factor (Munroe *et al.*, 2000). The aggregation of hypertension in families explains the role of genes in the development of hypertension. The heritability of blood pressure has been estimated to be 0.6% (Lewis, 2007). Non genetics factors that might increase the risk of developing hypertension are obesity, high alcohol consumption, high salt intake, stress and smoking (Carretero *et al.*, 2000). There are two basic strategies for the genetic analysis of complex diseases, whole-genome scan and candidate gene analysis (Schork, 1997). The term whole-genome scan is screening for any variations that are present throughout the entire genome without prior

knowledge about the variations, while in candidate gene analysis a known gene or variation is analyzed to see whether they are associated with a disease phenotype. To date, finding the susceptibility loci for complex diseases has been less successful than the other disorders. This is due to the complicated architecture of complex diseases such as locus heterogeneity, age-dependent penetrance, gene-gene and gene-environmental interaction (Schork, 1997). Gene-gene interaction or epistasis is one of the interests of the current research in the field of human genetics. Large number of research has been conducted to investigate epistasis in human complex diseases such as cancer, diabetes and hypertension (Cordell, 2002).

The most stable variation of the genome occurs in the form of single nucleotide polymorphisms (SNPs) which make 90% of the common variations in the genome (Doris, 2002). In recent years SNPs have been postulated as the next generation for the identification of loci associated with complex diseases (Lai, 2001). SNPs association studies have revealed promising results in the genetic studies of complex diseases. Several candidate genes have been hypothesized to play a role in the development of hypertension. These genes encode proteins known to be involved in blood pressure regulation. Among these genes are the β2 adrenoceptor and dopamine receptor genes (Agarwal *et al.*, 2005). Sympathetic nervous system plays a major role in blood pressure regulation. Therefore genes coding for major proteins of the sympathetic nervous system were proposed as candidate genes for the genetic study of hypertension. β2 adrenoceptor is a G-protein couple receptor that upon activation by catecholamine increases the intracellular second messenger cyclic Adenosine Monophosphate (cAMP). β2 adrenoceptor mediates vasodilatation that is important

in blood pressure control. Other blood pressure regulating effects of β2 adrenoceptor include renal sodium handling and control of renin release (Pereira *et al.*, 2003).

Three common SNPs of β2 adrenoceptor are functionally important. The Arginine substitute by Glycine at nucleotide 16 (Arg16Gly) (rs1042714), the Glutamine substitution by Glutamic acid at nucleotide number 27 (Gln27Glu) (rs1042714) and Threonine substitution by Isoleucine at nucleotide number 164 (Thr164Ile) (rs1800888). These genetic variations might influence the receptor function and/or gene expression and hence contribute to the pathophysiology of several diseases such as hypertension. These polymorphisms have been studied in relation to hypertension and related conditions in different populations with conflicting results (Candy *et al.*, 2000; Kotanko *et al.*, 1997; Large *et al.*, 1997; Masuo *et al.*, 2005; Sethi *et al.*, 2005).

Dopamine is a precursor of noradrenalin and adrenaline. It is an endogenous neurotransmitter which modulates behavior, ion transport, vascular tone and blood pressure (Fang *et al.*, 2005). Dopamine receptor genes polymorphisms have been hypothesized to be involved in pathogenesis of essential hypertension (Agarwal *et al.*, 2005). Dopamine receptor D1 is found on the smooth muscle of renal arteries, juxtaglomerular apparatus and on renal tubules, whereas D2 receptor is present in intimal layer of renal vasculature, glomeruli, sympathetic nerve terminal and renal tubule (Fang *et al.*, 2005; Hussain & Lokhandwala, 2003). A study revealed alteration of renal sodium handling associated with certain polymorphisms of *DRD1* gene (Sato *et al.*, 2000). These polymorphisms might impair the receptor or function which will disrupt the sodium excretion and hence increase in blood pressure in certain individuals. In this study the *DRD1* and *DRD*2 polymorphisms A48G

(rs4532) and *Taq*1 A (re1800497) will be analyzed respectively. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) is a simple laboratory technique for the detection of genetic variants. It is easy, cost-effective accurate and commonly used for SNPs detection (Barnes, 2010). In PCR-RFLP, a segment of nucleic acid (in which the mutation is detected) is amplified then digested into different segment using the restriction enzyme, and then the product will be separated on agarose gel electrophoresis for mutation analysis. This case-control study aims to compare allele frequencies between cases and control subjects. Cases are individuals diagnosed with the disease (hypertension) and controls are healthy individuals. Both groups will be selected randomly based on specific inclusion and exclusion criteria. The increase in the frequency of the SNP allele in the cases compared to the controls will indicate that the SNP could be a risk factor for the hypertension among Malaysians.

Problem Statement

According to The Third National Health and Morbidity Survey of 2006, the prevalence of hypertension among Malaysian adults who are 39 years old or above is 43% (CPG, 2008). This rapid increase in the prevalence of hypertension will eventually lead to increase in the cardiovascular events associated with hypertension. According to the Information and Documentation Unit of the Ministry of Health of Malaysia, cardiovascular diseases are the major cause of 23-26% of death in government hospitals from 1994 to 2001 (Zambahari, 2004). Despite the high prevalence of hypertension in Malaysia, there is still lack of sufficient information on the most susceptible loci with hypertension among Malaysians.

Few years back there has been an increasing interest in genetic association studies of human hypertension. Several genes that involve in hypertension modulation such as β2 adrenoceptor and dopamine receptor have been screened for possible variation that can contribute to the pathology of hypertension in different population (Large *et al.*, 1997; Sato *et al.*, 2000; Thomas *et al.*, 2001). However, there is controversy in the results obtained from those studies and majority of these studies did not evaluate any possible interaction between different candidate genes. Hence, more studies using different population are needed in order to provide more information on genetic susceptibility of hypertension. Furthermore, to our knowledge there are no published work on the association analysis of β2 and dopamine receptor genes polymorphism and interactions between these genes in relation to hypertension among Malaysians.

Study Hypothesis

β 2 adrenoceptor and dopamine receptor gene polymorphisms are associated with Malaysian hypertensive subjects

Study Objectives:

Main Objectives

To determine the association between β2 adrenoceptor and dopamine receptor gene polymorphisms in Malaysian hypertensive subjects

Specific Objectives

1. To determine the association and allelic frequency of β2 adrenoceptor gene (*ADRB2*) Arg16Gly, Gln27Glu and Thr164Ile polymorphisms with hypertension in Malaysian subjects
2. To determine the association and allelic frequency of A48G and *Taq*1 A polymorphism of *DRD1* and *DRD2* respectively polymorphisms with hypertension in Malaysian subjects
3. To correlate β2 adrenoceptor and dopamine receptor gene polymorphisms with risk factors for hypertension
4. To examine possible interaction between polymorphisms of β2 adrenoceptor gene and Dopamine gene.

REFERENCES

Adrenergic beta-2- receptor surface, http://www.genecards.org/cgibin/carddisp.pl?gene=ADRB2&search=ADRB2

Agarwal, A., Williams, G. H., & Fisher, N. D. L. (2005). Genetics of human hypertension. *Trends in endocrinology and metabolism*, *16*(3), 127–133.

Alfredo, M., Rosana, F., Regina, C., Raphael, N., Airlane, A., José, K., & Alexandre, P. (2009). Beta-2 adrenergic receptor gene polymorphisms Gln27Glu, Arg16Gly in patients with heart failure. *BMC Cardiovascular Disorders*, *9*(1).

Antic, V., Dulloo, A., & Montani, J. P. (2003). Multiple mechanisms involved in obesity-induced hypertension. *Heart, Lung and Circulation*, *12*(2), 84–93.

Apalasamy, Y. D., Ming, M. F., Rampal, S., Bulgiba, A., & Mohamed, Z. (2011). Gender-Dependent Association of a beta2- Adrenergic Gene Variant With Obesity Parameters in Malaysian Malays. *Asia Pac J Public Health*, *23*, 23.

Apter, C. H. (2008). Genetic approches to human disease. *Genetic Diseases of the Kidney*.

Barnes, M. R. (2010). Genetic variation analysis for biomedical researchers: a primer. *Methods Mol.Biol*, *628*, 1–20.

Beevers, G., Lip, G. Y. H., & O'Brien, E. (2001). ABC of hypertension: the pathophysiology of hypertension. *BMJ: British Medical Journal*, *322*(7291), 912.

Beige, J., Bellmann, A., Sharma, A. M., & Geßner, R. (2004). Ethnic origin determines the impact of genetic variants in dopamine receptor gene (DRD1) concerning essential hypertension. *American journal of hypertension*, *17*(12), 1184–1187.

Bengtsson, K., Orho-Melander, M., Melander, O., Lindblad, U., Ranstam, J., Råstam, L., & Groop, L. (2001). ß2-Adrenergic receptor gene variation and hypertension in subjects with type 2 diabetes. *Hypertension*, *37*(5), 1303–1308.

Bhupatiraju, C., Patkar, S., Pandharpurkar, D., Joshi, S., & Tirunilai, P. (2012). Association and Interaction of-58C> T and±9 bp Polymorphisms of BDKRB2 Gene Causing Susceptibility to Essential Hypertension. *Clinical and Experimental Hypertension*, *34*(3), 230–235.

Brodde, O. E. (2008). β-1 and β-2 adrenoceptor polymorphisms: Functional importance, impact on cardiovascular diseases and drug responses. *Pharmacology & Therapeutics*, 1–29.

CPG, Malaysia of Health Malaysia (2004). *Clinical Practice Guidelines on Management of Obesity*.

Candy, G., Samani, N., Norton, G., Woodiwiss, A., Radevski, I., Wheatley, A., Cockcroft, J., & Hall, I. P.. (2000). Association analysis of [beta] 2 adrenoceptor polymorphisms with hypertension in a Black African population. *Journal of hypertension*, *18*(2), 167.

Cardon, L. R., & Bell, J. I. (2001). Association study designs for complex diseases. *Nature Reviews Genetics*, *2*(2), 91–99.

Carey, R. M. (2008). Pathophysiology of primary hypertension. *Comperhennsive Physiology*,

Carretero, O. A., & Oparil, S. (2000). Essential hypertension: Part I: definition and etiology. *Circulation*, *101*(3), 329.

Cho, Y. M., Ritchie, M. D., Moore, J. H., Park, J. Y., Lee, K. U., Shin, H. D., Lee, H. K., & Park, K. S. (2004). Multifactor-dimensionality reduction shows a two-locus interaction associated with Type 2 diabetes mellitus. *Diabetologia*, *47*(3), 549–554.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., Jones, D. W., Materson, B. J., Oparil, S., & Wright Jr. JT. (2003). The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, *289*(19), 2560–2572.

Chockalingam, A. (2008). World Hypertension Day and global awareness. *The Canadian journal of cardiology*, *24*(6), 441.

Cichon, S., Nöthen, M. M., Erdmann, J., & Propping, P. (1994). Detection of four polymorphic sites in the human dopamine D1 receptor gene (DRD1). *Human molecular genetics*, *3*(1), 209.

Cipolletta, Ersilia, Ciccarelli, M., Izzo, R., Immunologiche, C., & Ii, F. (2012). A polymorphism within the promoter of the dopamine receptor d1 (drd1 -48a / g) associates with impaired kidney function in white hypertensive patients. *Translational Medicine*, *2*(2), 10–19.

Cordell, H. J. (2002). Epistasis: what it means, what it doesn't mean, and statistical methods to detect it in humans. *Human molecular genetics*, *11*(20), 2463.

D.Ge, J.Huang, J.He, B.Li, X.Duan, R.Chen, & D.Gu. (2005). beta2-Adrenergic receptor gene variations associated with stage-2 hypertension in northern Han Chinese. *Annals of human genetics*, *69*(Pt 1), 36–44.

Delles, C., McBride, M. W., Graham, D., Padmanabhan, S., & Dominiczak, A. F. (2010). Genetics of hypertension: from experimental animals to humans. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1802*(12), 1299–1308.

Doris, P. A. (2002). Hypertension genetics, single nucleotide polymorphisms, and the common disease: common variant hypothesis. *Hypertension*, *39*(2), 323.

Duan, J., Wainwright, M. S., Comeron, J. M., Saitou, N., Sanders, A. R., Gelernter, J., & Gejman, P. V. (2003). Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Human molecular genetics*, *12*(3), 205–216.

Fang, Y. J., Thomas, G. N., Xu, Z. L., Fang, J. Q., Critchley, J. A. J. H., & Tomlinson, B. (2005). An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqI polymorphism and obesity and hypertension. *International journal of cardiology*, *102*(1), 111–116.

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults. *JAMA: the journal of the American Medical Association*, *287*(3), 356-359

Flynn, I. Y. J. T. (2009). 61 Pathophysiology of Hypertension. In P. N. and N. Y. E.Avner, W.Harmon (Ed.), *Pediatric Nephrology* (pp. 1485–1518). Springer.

Garland, E. M., & Biaggioni, I. (2001). Genetic polymorphisms of adrenergic receptors. *Clinical Autonomic Research*, *11*(2), 67–78.

Gong, M., & Hubner, N. (2006). Molecular genetics of human hypertension. *Clinical science*, *110*(Journal Article), 315–326.

Grandy, D. K., Zhou, Q. Y., Allen, L., Litt, R., Magenis, R. E., Civelli, O., & Litt, M. (1990). A human D1 dopamine receptor gene is located on chromosome 5 at q35. 1 and identifies an EcoRI RFLP. *American Journal of Human Genetics*, *47*(5), 828.

Grevle, L., Güzey, C., Hadidi, H., Brennersted, R., Idle, J. R., & Aasly, J. (2000). Allelic association between the DRD2 TaqI A polymorphism and Parkinson's disease. *Movement disorders*, *15*(6), 1070–1074.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., Gordon, D. J., Krauss, R. M., Savage, P. J., & Smith Jr, S. C. (2005). Diagnosis and management of the metabolic syndrome. *Circulation*, *112*(17), 2735–2752.

Gu, D., Reynolds, K., Wu, X., Chen, J., Duan, X., Muntner, P., Huang, G., Reynolds, R. F., Su, S., & Whelton, P. K. (2002). Prevalence, awareness, treatment, and control of hypertension in China. *Hypertension*, *40*(6), 920–927.

Hahn, L. W., Ritchie, M. D., & Moore, J. H. (2003). Multifactor dimensionality reduction software for detecting gene–gene and gene–environment interactions. *Bioinformatics*, *19*(3), 376–382.

Haines, J. L., & Pericak-Vance, M. A. (2006). *Genetic analysis of complex diseases*. Hoboken, N.J.: Wiley-Liss.

Hall, I. P. (1996). Beta 2 adrenoceptor polymorphisms: are they clinically important? *Thorax*, *51*(4), 351.

Hall, I. P. (2009). How will genetic approaches assist in the management of respiratory diseases? *Current opinion in pharmacology*, *9*(3), 256–261.

Halperin, R. O., Sesso, H. D., Ma, J., Buring, J. E., Stampfer, M. J., & Michael Gaziano, J. (2006). Dyslipidemia and the risk of incident hypertension in men. *Hypertension*, *47*(1), 45–50.

Hanchard, N. A. (2005). Genetic susceptibility and single-nucleotide polymorphisms. *Seminars in Fetal and Neonatal Medicine* (3rd ed., Vol. 10, pp. 283–289). Elsevier.

Haney, M., Ward, A. S., Foltin, R. W., & Fischman, M. W. (2001). Effect of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology*, *155*(4), 330–337.

Harvey, J. N., Worth, D. P., Brown, J., & Lee, M. R. (1985). The effect of oral fenoldopam (SKF 82526-J), a peripheral dopamine receptor agonist, on blood pressure and renal function in normal man. *British journal of clinical pharmacology*, *19*(1), 21.

Hata, A. (1995). Role of angiotensinogen in the genetics of essential hypertension. *Life Sciences*, *57*(26), 2385–2395.

Hauser, E. R., Pericak-Vance, M. A., & Am Heart, J. (2000). Genetic analysis for common complex disease. *American heart journal*, *140*(4), S36–44.

He, H., Oetting, W., Brott, M., & Basu, S. (2009). Power of multifactor dimensionality reduction and penalized logistic regression for detecting gene-gene interaction in a case-control study. *BMC medical genetics*, *10*(1), 127.

Hellström, L., Large, V., Reynisdottir, S., Wahrenberg, H., & Arner, P. (1999). The different effects of a Gln27Glu β2-adrenoceptor gene polymorphism on obesity in males and in females. *Journal of internal medicine*, *245*(3), 253–259.

Hirschhorn, J. N. (2005). Genetic approaches to studying common diseases and complex traits. *Pediatric research*, *57*(5 Part 2), 74R.

Hopkins, P. N., & Hunt, S. C. (2003). Genetics of hypertension. *Genetics in Medicine*, *5*(6), 413.

Huang, P. L. (2009). A comprehensive definition for metabolic syndrome. *Disease Models & Mechanisms*, *2*(5-6), 231.

Hussain, T., & Lokhandwala, M. F. (2003). Renal dopamine receptors and hypertension. *Experimental biology and medicine*, *228*(2), 134–142.

Ibrahim, N. N. I. N., Rasool, A. H. G., Wong, A. R., & Abdul Rahman, A. R. (2009). Prevalence of [beta]-2 adrenergic receptor ([beta] 2AR) polymorphisms and its influence on a model used to assess endothelial function using pulse wave analysis (PWA). *Clinica Chimica Acta*, *409*(1-2), 62–66.

Jenei, Z., Pall, D., Katona, E., Kakuk, G., & Polgár, P. (2002). The epidemiology of hypertension and its associated risk factors in the city of Debrecen, Hungary. *Public health*, *116*(3), 138–144.

Johnson, J. A. (2003). Pharmacogenetics: potential for individualized drug therapy through genetics. *TRENDS in Genetics*, *19*(11), 660–666.

Kaplan, N. M. (1998). The 6th joint national committee report (JNC-6): new guidelines for hypertension therapy from the USA. *The Keio journal of medicine*, *47*(2), 99–105.

Kato, N., Sugiyama, T., Morita, H., Kurihara, H., Sato, T., Yamori, Y., & Yazaki, Y. (2001). Association analysis of ß2-adrenergic receptor polymorphisms with hypertension in Japanese. *Hypertension*, *37*(2), 286–292.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. *The Lancet*, *365*(9455), 217–223.

Kim, S., & Misra, A. (2007). SNP genotyping: technologies and biomedical applications. *Annu.Rev.Biomed.Eng.*, *9*(Journal Article), 289–320.

Kiryluk, K. (2009). Renal function and genetic variation in dopamine D1 receptor: is the case strong enough?. *Kidney international*, *76*(10), 1019–1022.

Kohara, K., Tabara, Y., Nakura, J., Imai, Y., Ohkubo, T., Hata, A., Soma, M., Nakayama, T., Umemura, S., & Hirawa, N. (2008). Identification of hypertension-susceptibility genes and pathways by a systemic multiple candidate gene approach: the millennium genome project for hypertension. *Hypertension Research*, *31*(2), 203–212.

Koivukoski, L., Fisher, S. A., Kanninen, T., Lewis, C. M., Von Wowern, F., Hunt, S., Kardia, S. L. R., Levy, D., Perola, M., & Rankinen, T. (2004). Meta-analysis of genome-wide scans for hypertension and blood pressure in Caucasians shows evidence of susceptibility regions on chromosomes 2 and 3. *Human molecular genetics*, *13*(19), 2325–2332.

Kotanko, P., Binder, A., Tasker, J., DeFreitas, P., Kamdar, S., Clark, A. J. L., Skrabal, F., & Caulfeild, M. (1997). Essential hypertension in African Caribbeans associates with a variant of the ß2-adrenoceptor. *Hypertension*, *30*(4), 773–776.

Kuchel, O. G., & Kuchel, G. A. (1991). Peripheral dopamine in pathophysiology of hypertension. Interaction with aging and lifestyle. *Hypertension*, *18*(6), 709–721.

Lai, E. (2001). Application of SNP technologies in medicine: lessons learned and future challenges. *Genome research*, *11*(6), 927.

Large, V., Hellström, L., Reynisdottir, S., Lönnqvist, F., Eriksson, P., Lannfelt, L., & Arner, P. (1997). Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function. *Journal of Clinical Investigation*, *100*(12), 3005.

Lawler, K. A., Kline, K., Seabrook, E., Krishnamoorthy, J., Anderson, S. F., Wilcox, Z. C., Craig, F., Adlin, R., Thomas, S. (1998). Family history of hypertension: a psychophysiological analysis. *International Journal of Psychophysiology*, *28*(2), 207–222.

Lee, Y. W., Oh, V., Garcia, E., Taylor, E. A., Wu, H., Yap, E. P. H., Kazeem, G. R., Caulfeild, M. J., & Munroe, P. B. (2004). Haplotypes of the [beta] 2-adrenergic receptor gene are associated with essential hypertension in a Singaporean Chinese population. *Journal of hypertension*, *22*(11), 2111.

Leineweber, K, & Brodde, O. E. (2004). beta 2-adrenoceptor polymorphisms: Relation between in vitro and in vivo phenotypes. *Life Sciences*, *74*(23), 2803–2814.

Leineweber, K, & Heusch, G. (2009). b1- and b2-Adrenoceptor polymorphisms and cardiovascular diseases. *British Journal of Pharmacology*, *158*, 61–69.

Lewis, C. M. (2002). Genetic association studies: design, analysis and interpretation. *Briefings in bioinformatics*, *3*(2), 146–153.

Lewis, R. (2007). *Human genetics : concepts and applications*. Boston: McGraw-Hill.

Li, X. X., Bek, M., Asico, L. D., Yang, Z., Grandy, D. K., Goldstein, D. S., Rubinstein, M., Eisner, G. M., & Jose, P. A. (2001). Adrenergic and endothelin B receptor-dependent hypertension in dopamine receptor type-2 knockout mice. *Hypertension*, *38*(3), 303–308.

Lifton, R P. (1995). Genetic determinants of human hypertension. *Proceedings of The National Academy of Sciences*, *92*(19), 8545.

Lifton, Richard P, & Boyden, L. M. (2008). Genetic Approaches to Human Disease. *Genetic Diseases of the Kidney*. Retrieved from http://books.google.com/books

Liu, W., Zhao, W., & Chase, G. A. (2004). Genome scan meta-analysis for hypertension. *American journal of hypertension*, *17*(12), 1100–1106.

Lou, Y., Liu, J., Li, Y., Liu, Y., Wang, Z., Liu, K., Wu, H., Niu, Q., Gu, W., Guo, Y., & Li, Z. (2011). Association study of the β2-adrenergic receptor gene polymorphisms and hypertension in the Northern Han Chinese. *PloS one*, *6*(4), 8.

Lynch, A. I., Tang, W., Shi, G., Devereux, R. B., Eckfeldt, J. H., & Arnett, D. K. (2011). Epistatic effects of ACE I/D and AGT gene variants on left ventricular mass in hypertensive patients: the HyperGEN study. *Journal of human hypertension*, *26*(2), 133–140.

MOH. (2008). *Clinical Practice Guidelines on Management of Hypertension. 3rd*.

Mahley, R. W., Innerarity, T. L., Rall Jr, S. C., & Weisgraber, K. H. (1984). Plasma lipoproteins: apolipoprotein structure and function. *Journal of lipid research*, *25*(12), 1277–1294.

Malaysia at Glance. (2010). Retrieved June 6, 2012, from http://www.statistics.gov.my

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., McCarthy, M. I., Ramos, E. M., Cardon, L.R., & Chakravati. A. (2009). Finding the missing heritability of complex diseases. *Nature*, *461*(7265), 747–753.

Martínez, J. A., Corbalán, M. S., Sánchez-Villegas, A., Forga, L., Marti, A., & Martínez-González, M. A. (2003). Obesity Risk Is Associated with Carbohydrate Intake in Women Carrying the Gln27Glu ß2-Adrenoceptor Polymorphism. *The Journal of nutrition*, *133*(8), 2549–2554.

Masuo, K., Katsuya, T., Fu, Y., Rakugi, H., Ogihara, T., & Tuck, M. L. (2005). β2-and β3-adrenergic receptor polymorphisms are related to the onset of weight gain and blood pressure elevation over 5 years. *Circulation*, *111*(25), 3429–3434.

Mathur, V. S., Swan, S. K., Lambrecht, L. J., Anjum, S., Fellmann, J., McGuire, D., Epstein, M., & Luther, R. R. (1999). The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. *Critical Care Medicine*, *27*(9), 1832.

Mei, H., Cuccaro, M. L., & Martin, E. R. (2007). Multifactor Dimensionality Reduction–Phenomics: A Novel Method to Capture Genetic Heterogeneity with Use of Phenotypic Variables. *The American Journal of Human Genetics*, *81*(6), 1251–1261.

Mikhail, N., Golub, M. S., & Tuck, M. L. (1999). Obesity and hypertension. *Progress in cardiovascular diseases*, *42*(1), 39–58.

Miller, M. S., & Cronin, M. T. (2000). *Genetic polymorphisms and susceptibility to disease*. London; New York: Taylor & Francis.

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G. (1998). Dopamine receptors: from structure to function. *Physiological Reviews*, *78*(1), 189–225.

Moffatt, R. J., & Stamford, B. A. (2006). *Lipid metabolism and health*. Boca Raton, FL: CRC/Taylor & Francis.

Mohamud, W. N. W., Musa, K. I., Khir, A. S. M., Ismail, A. S., Ismail, I. S., Kadir, K. A., Kamaruddin, N. A., Yaacob, N. A., Mustafa, N., & Ali, O . (2011). Prevalence of overweight and obesity among adult Malaysians: an update. *Asia Pac J Clin Nutr*, *20*(1), 35–41.

Moore, J. H., Gilbert, J. C., Tsai, C. T., Chiang, F. T., Holden, T., Barney, N., & White, B. C. (2006). A flexible computational framework for detecting, characterizing, and interpreting statistical patterns of epistasis in genetic studies of human disease susceptibility. *Journal of theoretical biology*, *241*(2), 252–261.

Munroe, P. B., & Caulfield, M. J. (2000). Genetics of hypertension. *Current Opinion in Genetics & Development*, *10*(3), 325–329.

Minor allele frequencies of ADRB2 polymorphisms, http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1042714 http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1042713 http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1800888

Neve, K. A. (2005). Dopamine Receptors. *Dopamine and glutamate in psychiatric disorders*, (Journal Article), 3–43.

Ota, M., Fukushima, H., Kulski, J. K., & Inoko, H. (2007). Single nucleotide polymorphism detection by polymerase chain reaction-restriction fragment length polymorphism. *Nature protocols*, *2*(11), 2857–2864.

Paneth, N., Susser, E., & Susser, M. (2002). Origins and early development of the case-control study: part 1, Early evolution. *Sozial-und Präventivmedizin/Social and Preventive Medicine*, *47*(5), 282–288.

Park, H. S., Shin, E. S., & Lee, J. E. (2008). Genotypes and haplotypes of [beta] 2-adrenergic receptor and parameters of the metabolic syndrome in Korean adolescents. *Metabolism*, *57*(8), 1064–1070.

Pattin, K. A., White, B. C., Barney, N., Gui, J., Nelson, H. H., Kelsey, K. T., Andrew, A. S., Karagas, & M. R., Moore, J. H. (2009). A computationally efficient hypothesis testing method for epistasis analysis using multifactor dimensionality reduction. *Genetic epidemiology*, *33*(1), 87–94.

Pereira, A. C., Floriano, M. S., Mota, G. F. A., Cunha, R. S., Herkenhoff, F. L., Mill, J. G., & Krieger, J. E. (2003). {beta} 2 Adrenoceptor Functional Gene Variants, Obesity, and Blood Pressure Level Interactions in the General Population. *Hypertension*, *42*(4), 685.

Rampal, L., Rampal, S., Azhar, M. Z., & Rahman, A. R. (2008). Prevalence, awareness, treatment and control of hypertension in Malaysia: A national study of 16,440 subjects. *Public health*, *122*(1), 11–18.

Ranade, K., Shue, W. H. H., Hung, Y. J., Hsuing, C. A., Chiang, F. T., Pesich, R., Hebert, J., Olivier, M., Chen, Y. D. I., & Pratt, R. (2001). The glycine allele of a glycine/arginine polymorphism in the β2-adrenergic receptor gene is associated with essential hypertension in a population of Chinese origin. *American journal of hypertension*, *14*(12), 1196–1200.

Ritchie, M. D., & Motsinger, A. A. (2005). Multifactor dimensionality reduction for detecting gene–gene and gene–environment interactions in pharmacogenomics studies. *Pharmacogenomics*, *6*(8), 823–834.

Sato, M., Soma, M., Nakayama, T., & Kanmatsuse, K. (2000). Dopamine D1 receptor gene polymorphism is associated with essential hypertension. *Hypertension*, *36*(2), 183.

Schork, N. J. (1997). Genetics of complex disease. Approaches, problems, and solutions. *American journal of respiratory and critical care medicine*, *156*(4), S103.

Schork, N. J., Fallin, D., & Lanchbury, J. S. (2000). Single nucleotide polymorphisms and the future of genetic epidemiology. *Clinical genetics*, *58*(4), 250–264.

Schürks, M., Kurth, T., Ridker, P. M., Buring, J. E., & Zee, R. Y. L. (2009). Association between polymorphisms in the β2-adrenergic receptor gene with myocardial infarction and ischemic stroke in women. *Thrombosis and haemostasis*, *101*(2), 351.

Sesso, H. D., Buring, J. E., Chown, M. J., Ridker, P. M., & Gaziano, J. M. (2005). A prospective study of plasma lipid levels and hypertension in women. *Archives of Internal Medicine*, *165*(20), 2420.

Sethi, A. A., Tybjaerg-Hansen, A., Jensen, G. B., & Nordestgaard, B. G. (2005). 164Ile allele in the beta2-Adrenergic receptor gene is associated with risk of elevated blood pressure in women. The Copenhagen City Heart Study. *Pharmacogenetics and genomics*, *15*(9), 633–645.

Sharma, P., Fatibene, J., Ferraro, F., Jia, H., Monteith, S., Brown, C., Clayton, D., O'Shaughnessy, K., & Brown, M. J. (2000). A genome-wide search for susceptibility loci to human essential hypertension. *Hypertension*, *35*(6), 1291–1296.

Silverman, E. K., & Palmer, L. J. (2000). Case-Control Association Studies for the Genetics of Complex Respiratory Diseases. *American Journal of Respiratory Cell and Molecular Biology*, *22*(6), 645–648.

Singh, R. B., Suh, I. L., Singh, V. P., Chaithiraphan, S., Laothavorn, P., Sy, R. G., Babilonia, N. A., Rahman, A. R. A., Sheikh, S., & Tomlinson, B. (2000). Hypertension and stroke in Asia: prevalence, control and strategies in developing countries for prevention. *Journal of human hypertension*, *14*(10-11), 749–763.

Sleight, P. (1993). Smoking and hypertension. *Clin Exp Hypertens*, *15*(6), 1181-1192.

Smith, D. J., & Lusis, A. J. (2009). Genomic Approaches to Complex Disease. In W. & Ginsburg (Ed.), *Genomic and Personalized Medicine* (pp. 33–46). Elsevier Inc.

Smith, D. J., & Lusis, A. J. (2009b). Genomic approches to complex diseases, 33–46.

Staessen, J. A., Kuznetsova, T., Zhang, H., Maillard, M., Bochud, M., Hasenkamp, S., Westerkamp, J., Richart, T., Thijs. K., & Li, X. (2008). Blood pressure and renal sodium handling in relation to genetic variation in the DRD1 promoter and GRK4. *Hypertension*, *51*(6), 1643–1650.

Sunahara, R. K., Niznik, H. B., Weiner, D. M., Stormann, T. M., Brann, M. R., Kennedy, J. L., Gelernter, J. E., Rozmahel, R., Yang, Y., Israel, Y. (1990). Human dopamine D1 receptor encoded by an intronless gene on chromosome 5. *Nature*, 80–83.

Taylor, J. G., Choi, E. H., Foster, C. B., & Chanock, S. J. (2001). Using genetic variation to study human disease. *Trends in molecular medicine*, *7*(11), 507–512.

Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol. (2001). National Institute of Health, http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf

Thomas, G. N., Critchley, J. A. J. H., Tomlinson, B., Cockram, C. S., & Chan, J. C. N. (2001). Relationships between the taqI polymorphism of the dopamine D2 receptor and blood pressure in hyperglycaemic and normoglycaemic Chinese subjects. *Clinical endocrinology*, *55*(5), 605–611.

Timmermann, B., Mo, R., Luft, F. C., Gerdts, E., Busjahn, A., Omvik, P., Li, G. H., Schuster, H., Wienker, T. F., & Hoehe, M. R. (1998). &bgr;-2 Adrenoceptor genetic variation is associated with genetic predisposition to essential hypertension: The Bergen Blood Pressure Study. *Kidney international*, *53*(6), 1455–1460.

Tomaszewski, M., Brain, N. J., Charchar, F. J., Wang, W. Y., Lacka, B., Padmanabahn, S., Clark, J. S., Andreson, N. H., Edwards, H. V., Zukowska-Szczechowska, E., & Diminiczak, A. F. (2002). Essential hypertension and beta2-adrenergic receptor gene: linkage and association analysis. *Hypertension*, *40*(3), 286–291.

Tortora, G. J., & Grabowski, S. R. (2003). *Principles of anatomy and physiology*. New York: Wiley.

Tozawa, M., Oshiro, S., Iseki, C., Sesoko, S., Higashiuesato, Y., Tana, T., Ikemiya, Y., Iseki, K., & Fukiiyama, K.. (2001). Family history of hypertension and blood pressure in a screened cohort. *Hypertension research: official journal of the Japanese Society of Hypertension*, *24*(2), 93.

Understanding low blood pressure, http://www.webmd.com/heart/understanding-low-blood-pressure-basics

Virdis, A., Giannarelli, C., Fritsch Neves, M., Taddei, S., & Ghiadoni, L. (2010). Cigarette smoking and hypertension. *Current pharmaceutical design*, *16*(23), 2518–2525.

Von Wowern, F., Bengtsson, K., Lindgren, C. M., Orho-Melander, M., Fyhrquist, F., Lindblad, U., Råstam, L., Forsblom, C., Kanninen, T., Almgren, P. (2003). A genome wide scan for early onset primary hypertension in Scandinavians. *Human molecular genetics*, *12*(16), 2077–2081.

Whelton, P. K., He, J., & Muntner, P. (2004). Prevalence, awareness, treatment and control of hypertension in North America, North Africa and Asia. *Journal of human hypertension*, *18*(8), 545–551.

Wigginton, J. E., Cutler, D. J., & Abecasis, G. R. (2005). A note on exact tests of Hardy-Weinberg equilibrium. *The American Journal of Human Genetics*, *76*(5), 887–893.

Wolf-Maier, K., Cooper, R. S., Banegas, J. R., Giampaoli, S., Hense, H. W., Joffres, M., Kastarinen, M., Poulter, N., Prematesta, P., & Rodridguez-Artalejo, F. (2003). Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA: the journal of the American Medical Association*, *289*(18), 2363.

Wood, A. J. J., Murphy, M. B., Murray, C., & Shorten, G. D. (2001). Fenoldopam-a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *New England Journal of Medicine*, *345*(21), 1548–1557.

Xie, H. G., Stein, C. M., Kim, R. B., Xiao, Z. S., He, N., Zhou, H. H., Gainer, J. V., Brown, N. J., Haines, J. L., & Wood, A. J. J. (1999). Frequency of functionally important beta-2 adrenoceptor polymorphisms varies markedly among African-American, Caucasian and Chinese individuals. *Pharmacogenetics-london-*, *9*, 511–516.

Xu, J., Wiesch, D. G., & Meyers, D. A. (1998). Genetics of complex human diseases: genome screening, association studies and fine mapping. *Clinical and Experimental Allergy*, *28*, 1–5.

Yang, C. H., Cheng, Y. H., Chuang, L. Y., & Chang, H. W. (n.d.). A mismatch PCR-RFLP primer design for SNP genotyping using genetic algorithm. *Cognitive Informatics (ICCI), 2010 9th IEEE International Conference on* (pp. 143–148). IEEE.

Yugar-Toledo, J. C., Martin, J. F. V., Krieger, J. E., Pereira, A. C., Demacq, C., Coelho, O. R., Pimenta, E., Calhoun, D. A., & Junior, H. M. (2011). Gene Variation in Resistant Hypertension: Multilocus Analysis of the Angiotensin 1-Converting Enzyme, Angiotensinogen, and Endothelial Nitric Oxide Synthase Genes. *DNA and cell biology*, *30*(8), 555–564.

Zambahari, R. (2004). Trends in cardiovascular diseases and risk factors in Malaysia. *Atherosclerosis XIII. Proceedings of the 13th International Atherosclerosis Symposium*, *1262*, 446–449.

Zar, J. H. (1984). *Biostatistical analysis*. Englewood Cliffs, N.J.: Prentice-Hall.

Zeng, C, Sanada, H., Watanabe, H., Eisner, G. M., Felder, R. A., & Jose, P. A. (2004). Functional genomics of the dopaminergic system in hypertension. *Physiological genomics*, *19*(3), 233–246.

Zeng, Chunyu, Zhang, M., Asico, L. D., Eisner, G. M., & Jose, P. A. (2007a). The dopaminergic system in hypertension. *Clinical science*, *112*, 583–597.

Ziegler, A., König, I. R., & Thompson, J. R. (2008). Biostatistical Aspects of Genome-Wide Association Studies. *Biometrical Journal*, *50*(1), 8–28.

Zondervan, K. T. (2011). *Genetic Association Study Design* (pp. 25–48). UK: University of Oxford.