GENETIC ASSOCIATION STUDY OF KCNB1 GENE WITH THE SUSCEPTIBILITY OF HYPERTENSION RELATED LEFT VENTRICULAR HYPERTROPHY (LVH) PATIENTS IN MALAYSIA

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Contents

1. Letter of Report Submission

2. Letter of Offer (Research Grant)

3. Acknowledgements

We wish to thank the Malaysian Society of Hypertension (MSH) for providing this research fund; and the Institute of Medical Molecular Biotechnology (IMMB), Faculty of Medicine, UiTM, and the Research Management Institute UiTM, for the supports given throughout the study.

We appreciate all subjects who voluntarily and generously participated this study.

4. Enhanced Research Title and Objectives

Original Title as Proposed:
GENETIC ASSOCIATION STUDY OF KCNB1 GENE WITH THE SUSCEPTIBILITY OF HYPERTENSION RELATED LEFT VENTRICULAR HYPERTROPHY (LVH) PATIENTS IN MALAYSIA
Improved/Enhanced Title:

Original Objectives as Proposed:

i. To characterize the single nucleotide polymorphism (SNP) of the candidate gene KCNB1 among the hypertension related left ventricular hypertrophy in Malaysians
ii. To associate the SNP of the candidate gene KCNB1 with the susceptibility of LVH in the hypertension related LVH patients in Malaysia

Improved/Enhanced Objectives:

5. Report

5.1 Proposed Executive Summary

Left ventricular hypertrophy (LVH) is an independent risk factor for the development of heart failure, coronary heart disease and stroke. It develops as a result of hemodynamic overload, for instance, hypertension (Gary et al., 2007). Blood pressure is an important determinant of LVH, and significant proportion of patients with essential hypertension develops their complication. However, this disease varies in a wide range of phenotype, and studies had shown that patients with LVH may have near-normal blood pressure, suggesting that development of LVH may be an independent genetic factor from hypertension.

LVH can be reversed with anti-hypertensive (anti-HT) agents. Angiotensinogen receptor blocker like Losartan has been shown to improve the reversal effect. However, it is unknown whether using this anti-HT agent alone would be useful in preventing LVH. Hence, identifying HT patients with the risk of LVH may allow this hypothesis to be tested, and if successful, would lead to the prevention, treatment and improvement of prognosis of LVH.

A recent genome-wide association study (GWAS) has been carried out by HyperGEN study (Arnett et al., 2009). This study reported the involvement of a candidate gene KCNB1 located at chromosome 20q13.2. The protein produce of this gene is dephosphorylated by calcineurin, a gene well known to be associated with LVH (Tang et al., 2005), reflecting a unique mechanism for development of LVH in hypertension. However, whether the finding is relevant to the Southeast Asia populations or not remains to be validated, as the study was carried out in the Western populations, of which the allele frequencies and the linkage disequilibrium (LD) structures are quite different between the two continents.

This proposed study hence, attempts to verify the study by replicating the finding in our population, ie studying the SNPs of the KCNB1 gene among the hypertensive patients with LVH.

5.2 Enhanced Executive Summary

Left ventricular hypertrophy (LVH) is an independent risk factor for the development of heart failure, coronary heart disease and stroke. It develops as a result of hemodynamic overload, for instance, hypertension [1, 2]. Blood pressure is an important determinant of LVH, and a significant proportion of patients with essential hypertension develops this complication. However, this condition varies in a wide range of phenotypes, and studies had shown that patients with LVH may have near-normal blood pressure, suggesting that development of LVH may be due to an independent genetic factor from hypertension [3].

LVH can be reversed with anti-hypertensive (anti-HT) agents. Angiotensinogen receptor blocker like losartan has been shown to improve the reversal effect [4-6]. However, it is unknown whether using this anti-HT agent alone would be useful in preventing LVH. Hence, identifying HT patients with the risk of LVH may allow this hypothesis to be tested, and if successful, would lead to the prevention, treatment and improvement of prognosis of LVH.

The normal distribution of LV mass (as an indicator of LVH) in the population indicates the involvement of complex and multiple genetic factors to the trait. Various genetic studies had been carried out extensively, reporting mainly on the candidate genes like angiotensin converting enzyme (ACE), guanine nucleotide-binding protein gene (GNB3), insulin-like growth factor (IGF-1), angiotensin II (AGT II), angiotensin receptors (AGTRs) [7-12] etc but no conclusive result was obtained.

A recent genome-wide association study (GWAS) carried out by the HyperGEN study [13] reported the involvement of a candidate gene KCNB1 located at chromosome 20q13.2. found that SNP (rs756529) located in KCNB1 gene was associated with LV mass in European population. The protein produced by this gene is dephosphorylated by calcineurin, which is well known to be associated with LVH [14], reflecting a unique mechanism for development of LVH in hypertension. However, whether the finding is relevant to the Southeast Asia populations or not remains to be validated, as the study was carried out in the Western populations, of which the allele frequencies and the structure of linkage disequilibrium (LD) are known to be different between the two major continents.

This proposed study hence, attempts to verify the study by replicating the finding in our population, ie studying the SNPs of the KCNB1 gene among the hypertensive patients with LVH.

We have genotyped earlier 100 subjects on the SNP rs6063397. We noted that this SNP is in full linkage disequilibrium with rs756529 (D' = 1: r2 =1). Therefore in this study, we attempted to genotype rs6063397 in additional 100 subjects with hypertension and/or with left ventricular hypertrophy. Of the total 200 hypertensive subjects, 61 were LVH and 139 were non LVH. These subjects were genotyped using sequencing. No association was observed between both alleles and genotypes of rs6063397 LVH susceptibility suggesting that KCNB1 may not play role in LVH susceptibility in hypertensive patients in Southeast Asian populations.

5.3 Introduction

Left ventricular hypertrophy (LVH) is an independent risk factor for the development of heart failure, coronary heart disease and stroke. It develops as a result of hemodynamic overload, for instance, hypertension (Gary et al., 2007). Blood pressure is an important determinant of LVH, and significant proportion of patients with essential hypertension develops their complication. However, this disease varies in a wide range of phenotype, and studies had shown that patients with LVH may have near-normal blood pressure, suggesting that development of LVH may be an independent genetic factor from hypertension.

LVH can be reversed with anti-hypertensive (anti-HT) agents. Angiotensinogen receptor blocker like Losartan has been shown to improve the reversal effect. However, it is unknown whether using this anti-HT agent alone would be useful in preventing LVH. Hence, identifying HT patients with the risk of LVH may allow this hypothesis to be tested, and if successful, would lead to the prevention, treatment and improvement of prognosis of LVH.

Scientific Rationale:
The normal distribution of LV mass (as an indicator of LVH) in the population indicates the involvement of complex and multiple genetic factors to the trait. Various genetic studies had been carried out extensively, reporting mainly on the candidate genes like angiotensin converting enzyme (ACE), guanine nucleotide-binding protein gene (GNB3), insulin-like growth factor (IGF-1), angiotensin II (AGT II), angiotensin receptors (AGTRs) (Doolan et al., 2004; Semplicini et al., 2001; Nagy et al., 1999; Lindpaintner et al., 2004; Olszanecka et al., 2003; Jeunemaitre et al., 2008) etc but no conclusive result was obtained. Though, this may be more indicative of the nature of this complex disease.

A recent genome-wide association study (GWAS) has been carried out by HyperGEN study (Arnett et al., 2009). This study reported the involvement of a candidate gene KCNB1 located at chromosome 20q13.2. The protein produce of this gene is dephosphorylated by calcineurin, a gene well known to be associated with LVH (Tang et al., 2005), reflecting a unique mechanism for development of LVH in hypertension. However, whether the finding is relevant to the Southeast Asia populations or not remains to be validated, as the study was carried out in the Western populations, of which the allele frequencies and the linkage disequilibrium (LD) structures are quite different between the two continents.