UNDERSTANDING THE ROLE OF COPY NUMBER (CNV) IN THE DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION

RESEARCH MANAGEMENT INSTITUTE (RMI)
UNIVERSITI TEKNOLOGI MARA
40450 SHAH ALAM, SELANGOR
MALAYSIA

BY :

KHALID YUSOFF
HOH BOON PENG

DECEMBER 2012

Contents

Fakulti Perubatan
Faculty of Medicine

Universiti Teknologi MARA
Kampus Selayang,
Jalan Prima Selayang 7,
68100 Batu Caves,
Selangor Darul Ehsan, MALAYSIA
Tel : (+603) 6126 4800
Faks : (+603) 6126 4888
www.medic.uitm.edu.my

UNIVERSITI TEKNOLOGI MARA

PEMENANG
Anugerah Kualiti Perdana Menteri
2008

Date : 19 Dec 2012

YBrs. Professor Dr Abu Bakar Majeed
Penolong Naib Canselor
Institut Penyelidikan, Pembangunan dan Pengkomersilan (IDRC)
Universiti Teknologi MARA
40450 Shah Alam
Selangor Darul Ehsan

Prof,

RE: COMPLETION OF THE FRGS RESEARCH PROJECT: UNDERSTANDING THE ROLE OF COPY NUMBER VARIATION (CNV) IN THE DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION

With regards to the above mentioned matter, we are pleased to inform you that the project has been completed. The final report of this study is enclosed.

2. Briefly, we attempted to perform a genome-wide scan of rare copy number variation in 116 patients with hypertensive left ventricular hypertrophy. The subjects consisted of 44 LVH and 72 non LVH, and they were genotyped by using Illumina 660W-Quad SNP array. We managed to identify the rare CNVs which potentially contribute to the susceptibility of LVH, and we suggest that the non-canonical Wnt-signaling pathway may be an important contributor to the pathogenesis of this complication.

3. We have recruited 1 Research Assistant in this study. In addition, 2 manuscripts have been accepted for publication (Journal of Life Sciences, and BMC Molecular Cytogenetics). One abstract was presented in the HUGO2011 in Dubai. Another manuscript is ready to be submitted to a peer reviewed journal soon. Abstracts of the manuscripts are enclosed.

4. Further investigation with additional research funding is needed to warrant the finding of this study.

Thank you

Sincerely Yours,

Prof Dato' Dr Khalid Yusoff
Project Principle Investigator
Faculty of Medicine
Universiti Teknologi MARA, Sg Buloh Campus

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. 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.

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.

We recently carried out a genome-wide scan of copy number variation (CNV) on a group of hyptertensive LVH patients and observed a gain of copy number in AGTRII gene in a group of patients. We attempted to further investigate the role of CNV of this gene in the pathogenesis of LVH. However, we observed no significant contribution of this CNV in the disease complication.

Therefore in this study, we attempted to investigate the contributions of rare CNV in the susceptibility of hypertensive LVH, and subsequently to predict the putative molecular pathways in the pathogenesis of LVH.

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.

The impact of CNV in common and complex diseases has been well acknowledged since the last few years. However, its contribution to the cardiovascular disease such as hypertensive LVH has not been reported before. This proposed study hence, attempts to peform a genome-wide scan of CNV in patients with hypertensive LVH, and investigate the role of rare CNV in the susceptibility this complication.

Hypothesis:

We hypothesize that the rare CNVs contribute to the susceptibility of hypertensive LVH.