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UNIVERSITI TEKNOLOGI MARA

**MOLECULAR AND BIOCHEMICAL
STUDIES ON *FCGR1A*
SUSCEPTIBILITY IN DENGUE
INFECTION**

ZAIHARINA BINTI MOHAMAD ZAMBERI

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science

Faculty of Medicine

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated of acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

Name of Student : Zaiharina binti Mohamad Zamberi
Student I.D. No. : 2011821562
Programme : Master of Science (MD780)
Faculty : Medicine
Thesis Title : Molecular and biochemical studies on
FCGR1A susceptibility in dengue infection

Signature of Student



Date

June 2016

ABSTRACT

Dengue, a mosquito-borne viral disease is a serious public health concern in many countries around the world. In Malaysia, suspected cases of dengue infection increase dramatically every year. Dengue infections cause a variable spectrum of manifestations ranging from dengue fever (DF) to dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolaemic shock, called dengue shock syndrome (DSS). Recent studies suggested the potential role of Fc gamma receptors (FCGRs) in the pathogenesis of dengue. The aim of this study was to determine the frequencies of copy number variation (CNV) of the *FCGR1A* gene and correlate the *FCGR1A* profile with its gene expression and serum protein level in dengue patients with vascular leakage and those without vascular leakage. Extracted DNA, RNA and serum were isolated from blood and use to quantify *FCGR1A* CNV, gene expression and protein concentration using quantitative real-time polymerase chain reaction (qPCR), reverse transcription-qPCR (RT-qPCR) and enzyme-linked immunosorbent assay (ELISA) respectively. One hundred dengue patients with signs of vascular leakage (case) and without vascular leakage (control), and 50 healthy subjects (normal) tested. Statistical analysis revealed that CNV of *FCGR1A* was significantly associated with dengue when compared to the normal controls. The circulating Fc γ R1A were also found to be significantly different between dengue patients and normal controls. However, there was no difference between dengue patients and normal controls, and dengue patients with vascular leakage and those without vascular leakage. These findings suggested that the Fc γ R1A plays a role in the susceptibility of dengue infection, however, showed no evidence in contributing to the severity of dengue. Although the correlation between these three experiments were not significantly related, the role of *FCGR1A* in vascular leakage should not be excluded. Further studies with larger sample size is needed to confirm this finding.

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF STUDY

Dengue is one of the most important mosquito borne diseases and has become a major public health concern throughout the world (WHO, 2009). It is found largely in the areas of tropics and subtropics climate, and hot moist year (Ferreira, 2012). Dengue appears as endemic in Malaysia and many countries in the tropical and subtropical regions, predominantly in urban and semi-urban areas (WHO, 2009). This is mainly attributed to the uncontrolled dengue prevention and management, which consequently provides a suitable breeding habitat for the mosquitos (WHO 2009). The total of dengue cases has dramatically increased since the last few decades with increasing number of deaths. Globally, more than one-third of the world's population is living in areas at risk for transmission and infection of dengue fever (WHO, 2013).

The causative agent of dengue is dengue virus (DENV) containing a positive single-stranded RNA of approximately 11 kb in size (Stollar *et al.*, 1967). DENV comprises of four serotypes namely, *DENV1-DENV4*. Dengue virus belongs to a flavivirus family that is transmitted by the bite of an infected female mosquito *Aedes sp.* (in particular *Aedes aegypti*), as a vector for transmitting and spreading of the dengue fever. The mosquito usually bites at dusk and dawn even during the day. They prefer breeding areas at stagnant clean water such as flower pots, discarded tyres, wet shower floor and toilet tanks which allow the mosquito to breed in the residence. Currently there is no available vaccine for dengue, therefore effective prevention and control is required by reducing the habitat and the number of mosquitoes, and to limit exposure to *Aedes aegypti* bites.

Dengue infection induces a wide spectrum of clinical manifestations, ranging from asymptomatic to undifferentiated fever, dengue fever (DF) to dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolaemic shock, and dengue shock syndrome (DSS) (WHO, 1997). Despite difficulties in the use of DHF classification (Guha-Sapir and Schimmer, 2005; Deen *et al.*, 2006; Rigau-Perez, 2006), WHO had reclassified dengue into levels of severity by using a set of clinical