# FCGR3B GENE COPY NUMBER VARIATION AND HOST SUSCEPTIBILITY TO VASCULAR LEAKAGE IN DENGUE HEMORRHAGIC FEVER

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**KELULUSAN PERMOHONAN DANA KECEMERLANGAN FASA 03/2009**
**TAJUK PROJEK : *COPY NUMBER VARIATION OF FCGRII GENE AMONG THE DENGUE FEVER (DF) AND DENGUE HEMORRHAGIC FEVER (DHF) PATIENTS IN MALAYSIA***

Dengan segala hormatnya perkara di atas adalah dirujuk.

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# 5. Report

## 5.1 Proposed Executive Summary

DENV causes significantly more human disease than any other abovirus. Annually, an estimated of 50-100 million cases of severe dengue require hospitalization in which 500,000 resulted in DHF/DSS, with more than 20,000 death worldwide (WHO DengueNet report, 2005). Hence, it has now been recognized as a major expanding public health problem of the country. Dengue viruses cause a spectrum of illness ranging from asymptomatic infection or mild febrile illness to severe and fatal hemorrhagic disease. While majority experience uncomplicated Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) can present with severe clinical manifestations including transient vascular permeability resulting in plasma leakage (WHO, 1997). No specific treatment is available to date.

Previous studies suggested the involvement of the events in the peripheral blood in association with the DENV disease severity, such as dengue viral replication, cytokine expression, and cellular activation / proliferation and robust host inflammatory immune response (Rothman, 2004). Antibody-dependent enhancement of viral replication is the most widely accepted explanation for the association between DHF and pre-existing antibody. However, it remains considerable uncertainty as to how virus-host interaction triggers the inflammatory response resulting in plasma leakage, the hallmark of DHF/DSS.

FcGRII has been reported to play a role in pathogenesis of severe dengue infections (Loke et al., 2002; Littaua et al., 1990). It functions to mediate antibody enhancement *in vitro* by binding to virus-IgG complexes. A fundamental to any discussion of DENV pathogenesis is the association of secondary infection with heterologous serotypes with DHF/DSS. Antibody Dependent Enhancement (ADE) model during secondary infections, postulates that DENV specific antibodies either cross reactive antibodies, can interact with DENV without neutralizing the virus, and thereby requires FcG receptors to mediate entry of antibody coated DENV into cells (Clyde et al., 2006; Coffey et al., 2009).

Therefore, this proposed study investigated and to characterized the CNV of FcGRII gene among the DF and DHF patients. Though association of FcGRII gene SNP polymorphism with dengue has been reported earlier (Loke et al., 2002), none investigated the copy number of this gene and its association to the susceptibility of plasma leakage.

## 5.3 Introduction

Dengue viruses cause a spectrum of illness ranging from asymptomatic infection or mild febrile illness to severe and fatal hemorrhagic disease. While majority experience uncomplicated Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) can present with severe clinical manifestations including occurrence of vascular permeability defect resulting in plasma leakage, multifactorial haemostatic abnormalities (WHO, 1997). No specific treatment is available to date.

DENV causes significantly more human disease than any other abovirus. Annually, an estimated of 50-100 million cases of severe dengue require hospitalization of which 500,000 resulted in DHF/DSS, and more than 20,000 death worldwide. It has been documented that DENV is endemic in more than 100 countries, including most of the Southeast Asia, South and Central America, the Carribean and South Pacific regions, and DHF/DSS in more than 60 countries (WHO DengueNet report, 2005).

Previous studies suggested the involvement of the events in the peripheral blood in association with the DENV disease severity and outcome, such as dengue viral replication, cytokine expression, and cellular activation / proliferation (Rothman, 2004). Severe form of dengue infection has also been associated with robust host inflammatory immune response. Antibody-dependent enhancement of viral replication is the most widely accepted explanation for the association between DHF and pre-existing antibody. However, it remains considerable uncertainty as to how the virus-host interaction triggers the inflammatory response resulting in plasma leakage, the hallmark of DHF/DSS.

FcG receptor genes had been reported to play a role in antibody dependent enhancement (Kontny et al., 1988; Nielsen, 2009). One of the subclass of the FcGR gene cluster namely FcGR3B was suggested to mediate phagocytosis (Flesch et al., 1997) and uptake of immune complexes (Fanciulli et al., 2008; Wilcocks et al., 2008). Recent studies have associated this gene with a number of autoimmune diseases (reviewed by Fanciulli, 2007). To date no study was done on FcGR3B with dengue. A fundamental to any discussion of DENV pathogenesis is the association of secondary infection with heterologous serotypes with DHF/DSS. This has been evidenced by numerous studies that secondary infection is an important risk factor for severe disease, although there are occationally exceptional cases. Antibody Dependent Enhancement (ADE) model, postulates that some DENV specific antibodies either cross reactive antibodies, can interact with DENV without neutralizing the virus, and thereby