FCGR 3 B COPY NUMBER VARIATION AND HOST SUSCEPTIBILITY TO VASCULAR LEAKAGE IN DENGUE HEMORRHAGIC FEVER

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ABSTRACT

Introduction: Dengue is a serious public health threat in many countries around the world. It is estimated that 50-100 million cases of severe dengue requiring hospitalization occurs annually. Approximately 500,000 of these cases manifested as DHF/ Dengue Shock Syndrome (DSS) with more than 20, 000 deaths worldwide. Dengue deaths occur usually as a complication of severe vascular leakage. The mechanisms that lead to severe vascular leakage are still unknown. Recent studies suggested the potential role of Fc gamma receptors (FCGRs) in the pathogenesis of dengue. In the present study, copy number variation of the FCGR3B genes in a select dengue patient population in Malaysia is estimated. Methodology: Total cell DNA was extracted from dengue patients' whole blood. CNV genotyping was performed using the real time quantitative PCR (qPCR) with SYBR Green fluorescent dye assay (Bio Rad). In qPCR analysis, the relative quantification was used to analyse relative changes in CNV by comparing the fold change ratio of targeted gene and reference gene. Data from qPCR were analysed using Student t-test. Results: 120 patients diagnosed with dengue were included in this study. Ten patients were excluded because did not fit into the inclusion criteria, or low quality DNA yield. Fifty-seven were from patients who showed signs of vascular leakage (case) and fifty-three with typical dengue fever symptoms without vascular leakage (control). Results from the study suggested that 75% of the subjects showed normal FCGR3B copy number (CN = 2). Of the total 57 cases with vascular leakage, 5 had FCGR3B CN loss and 8 with CN gain. There was no significant association between CN loss and CN gain with vascular leakage when Chi-square analysis and logistic linear regression analysis was performed. Conclusion: The importance of FCGR in various autoimmune and inflammatory diseases has been well-documented. It is possible that the loss of FCGR3B could affect the antibody-dependent enhancement (ADE) of dengue in secondary infection resulting in reduced possibilities of induction of vascular leakage. Though no significant association was found, the role of FcGR3B CNV in vascular leakage during dengue infection should not be excluded. Further studies with much larger sample size however, is needed to confirm this finding.

1.1 Introduction

Dengue is a mosquito-borne viral disease and is transmitted principally by *Aedes aegypti* and *Aedes albopictus* (Kurane, 2007). The Dengue viruses (DENVs) belong to *Flaviruses* genus, of which there are four distinct serotypes (Dong et al., 2007). Infection with any of these viruses will cause a variable spectrum of disease that range from an undifferentiated fever to dengue fever through to the more severe syndromes called dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) {Guzman et al., 2007}

DENV infection has emerged as a major public health problem especially in the developing world (WHO, 1997). 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, 2009). In Malaysia, suspected cases of dengue infection increase dramatically every year. In year 2010, 46,171 cases were reported with 134 deaths where there is increment of 11% and 52% from the previous year (http://moh.gov.my/press_releases/). Dengue inflicts a significant health, economic and social burden on the population of endemic areas (WHO, 2009). Individuals and families are impacted by lost wages, cost of seeking care and treatment, missed school and extended effects of recovery (Potts et al., 2010). Moreover, this disease is potentially lethal, but only supportive measures are available (de Kruif et al., 2008). In addition, prevention and control have also been poorly implemented or unsustainable and thus largely ineffective (Potts et al., 2010).

DHF occurs almost exclusively in individuals with secondary heterologous DENV infections and infant with primary DENV infections born to dengue immune mother (Libraty et al., 2009). Unfortunately, the pathophysiology of DHF is still poorly understood. The key pathological feature of DHF is increased vascular permeability with plasma leakage into the interstitial spaces associated with increased level of vasoactive cytokines (Dong et al., 2007). Previous studies suggested numerous theories on how DHF/DSS develops in infected dengue individuals (Noisakran & Perng, 2008). As reviewed by Kurane, 2007 the theory of Antibody dependent enhancement (ADE) is the most widely accepted explanation for the association between DHF and pre-existing antibody. However, it remains considerable uncertainty and controversial as how antibodies enhance viral infection and how the virus-host interaction triggers the inflammatory response resulting in plasma leakage (Nielsen, 2009).

Fc gamma receptors (FcGRs) have been reported to play a role in antibody dependent enhancement (Kontny et al., 1988; Nielsen, 2009). These receptors are glycoproteins that bind the Fc portion of