UNIVERSITI TEKNOLOGI MARA

FCGR2A GENE COPY NUMBER VARIATION AND HOST SUSCEPTIBILITY TO VASCULAR LEAKAGE IN DENGUE INFECTION

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ABSTRACT

Dengue, the most rapidly spreading mosquito-borne viral disease in the world has been a major public health concern in Malaysia. According to the Ministry of Health, the incidence rate of dengue was 63.6 per 100 000 Malaysian population in 2011. Dengue deaths usually occur as a result of complication of severe vascular leakage. However, the exact mechanism of developing vascular leakage has still not been answered to universal satisfaction. Previous studies has reported the role of Fc gamma receptor 2A (FcGR2A) gene in mediating antibody dependent enhancement (ADE) pathway, leading to different clinical outcomes. In this study, we aimed to evaluate the association of FcGR2A gene copy number variation (CNV) with the presence of vascular leakage. The DNA was extracted from dengue patients' whole blood. CNV genotyping was employed by using quantitative PCR (qPCR) with TaqMan probe. The CNV calls that is CN normal, loss and gain were decided. Chi-square test was applied to determine the association of CNV calls with the susceptibility of vascular leakage. A total of 85 subjects were recruited (59 cases and 26 controls). We observed 19 subjects (13 cases, 6 controls) with CN gain. 11 subjects (7 cases, 4 controls) with CN loss. Whilst, the rest remained normal (CN=2). We suspect CNV of FcGR2A may not play a role in vascular leakage of dengue. Nonetheless, the hypothesis is not conclusive yet. Study with larger sample size and more advanced molecular technology are warranted to produce more convincing result.

1.1 Introduction

Dengue, the most rapidly spreading mosquito-borne viral disease in the world, is caused by dengue virus, the member of family flaviviridae (Shekhar, 1992). Dengue is a single stranded RNA (ribonucleic acid) virus with four antigenically distinct serotypes, dengue virus (DENV) 1-4 (Noisakran and Perng, 2008; Lin *et al.,* 2006). It is made up of three structural protein genes encoding the Core (C), Membrane (M) and Envelope (E); and seven non-structural proteins: NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5 (Kurane, 2007) (Figure 1). The dengue virus is transmitted into human by the mosquito *Aedes aegypti*, which is usually found in urban areas (Smith, 1956). About 50-100 million cases of severe dengue require hospitalization has been reported annually, of which, 500,000 resulted in Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS), with more than 20,000 death worldwide (WHO, 2009). DENV is endemic in more than 100 countries, including most of the Southeast Asia, the Carribean and South Pacific regions, South and Central America and DHF/DSS in more than 60 countries (WHO, 2001). It has been an important and major public health concern in Malaysia ever since its existence in 1902 (Skae, 1902). According to the Ministry of Health Malaysia in 2011, the incidence rate of dengue was 63.6 per 100,000 population. Nowadays, dengue infection is not a predominantly urban disease as it has expanded geographically into the rural areas. Nor Azila *et al.,* (2011) revealed that there was no difference in the dengue IgG seroprevalence between subjects staying in areas (92.03%) urban compared to those living in rural areas (90.95%). Approximately 92% subjects were found to be seropositive indicating that dengue might be endemic in Malaysia for a long time into the future.

Dengue infections are classified into asymtomatic and symptomatic with a wide range of clinical outcomes. Symptomatic infections could lead to undifferentiated fever, dengue fever (DF), or dengue hemorrhagic fever (DHF) (WHO, 2009). While majority experience uncomplicated DF, DHF can present with severe clinical manifestations including defect in vascular permeability resulting in plasma leakage and multifactorial haemostatic abnormalities (WHO, 1997). Most patients recover from self-limiting non-severe dengue, DF, but a small proportion of them progress into severe dengue DHF, which is manifested by accumulation of fluid in abdominal cavities and pleural cavities. This leakage will be resolved by spontaneous and rapid resolution within 48 hours, but when the leakage prolongs, it can cause intravascular volume and depletion in circulatory insufficiency (WHO, 2009). The extent of plasma leakage varies between individual