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Research paper

Divergence of the dengue virus type 2 Cosmopolitan genotype associated with two predominant serotype shifts between 1 and 2 in Surabaya, Indonesia, 2008–2014

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A B S T R A C T

Indonesia is one of the biggest dengue endemic countries, and, thus, is an important place to investigate the evolution of dengue virus (DENV). We have continuously isolated DENV in Surabaya, the second biggest city in Indonesia, since 2008. We previously reported sequential changes in the predominant serotype from DENV type 2 (DENV-2) to DENV type 1 (DENV-1) in November 2008 and from DENV-1 to DENV-2 in July 2013. The predominance of DENV-2 continued in 2014, but not in 2015. We herein phylogenetically investigated DENV-2 transitions in Surabaya between 2008 and 2014 to analyze the divergence and evolution of DENV-2 concomitant with serotype shifts. All DENV-2 isolated in Surabaya were classified into the Cosmopolitan genotype, and further divided into 6 clusters. Clusters 1–3, dominated by Surabaya strains, were defined as the "Surabaya lineage". Clusters 4–6, dominated by strains from Singapore, Malaysia, and many parts of Indonesia, were the "South East Asian lineage". The most recent common ancestor of these strains existed in 1988, coinciding with the time that an Indonesian dengue outbreak took place. Cluster 1 appeared to be unique because no other DENV-2 isolate was included in this cluster. The predominance of DENV-2 in 2008 and 2013–14 were caused by cluster 1, whereas clusters 2 and 3 sporadically emerged in 2011 and 2012. The characteristic amino acids of cluster 1, E-170 V and E-282Y, may be responsible for its prevalence in Surabaya. No amino acid difference was observed in the envelope region between strains in 2008 and 2013–14, suggesting that the re-emergence of DENV-2 in Surabaya was due to the loss or decrease of herd immunity in the 5-year period when DENV-2 subsided. The South East Asian lineage primarily emerged in Surabaya in 2014, probably imported from other parts of Indonesia or foreign countries.
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1. Introduction

Four serotypes of dengue virus (DENV-1 to −4) are distributed in tropical and sub-tropical regions and transmitted by the vector mosquitoes such as *Aedes aegypti* and *Aedes albopictus* (Halstead, 2008). DENV causes dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Halstead, 2007), or dengue and severe dengue classified by World Health Organization (WHO, 2012). More than 2.5 billion people are currently at risk of DENV infection, with 100 million people being estimated to be infected with DENV annually (Halstead, 2007). Furthermore, the incidence and geographical distribution of dengue have been increasing due to global warming and the rapid movement of viruses and vectors (Wilder-Smith and Gubler, 2008). Thus, DENV infection is regarded as a major public concern, especially in developing countries.

DENV belongs to the genus *Flavivirus* of the family *Flaviviridae*. The DENV genome encodes 3 structural proteins [capsid (C), pre-membrane (prM), and envelope (E)] and 7 non-structural (NS) proteins (Pierson and Diamond, 2013). Since the E protein is the major target of neutralizing antibodies, it is highly diverse and the main target region for phylogenetic analyses. There are three domains (domains I, II, and

Abbreviations: DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; C, capsid; prM, pre-membrane; E, envelope; NS, non-structural; NJ, neighbor-joining; MCMC, Markov Chain Monte Carlo; BEAST, Bayesian Evolutionary Analysis by Sampling Trees; MRCA, most recent common ancestor; BCI, bayesian credible interval; SEA, South East Asian.

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III) in the E protein structure (Modis et al., 2003). Previous studies revealed that the activities of neutralizing antibodies varied depending on the targeting domain (Heinz and Stiasny, 2012). Studies with mouse monoclonal antibodies (MAbs) have indicated that antibodies targeting domain III were able to interrupt viral attachment more efficiently than those targeting domains I-II (Sukupolvi-Petty et al., 2013). On the other hand, human antibodies targeting domain III do not play an important role in neutralization (Wahala and Silva, 2011; Williams et al., 2012). Further, studies with human MAb showed that domains I and II or their hinge regions contain strong neutralizing epitopes (de Alwis et al., 2012; Messer et al., 2014).

Four serotypes of DENV have been further classified into several genotypes based on the E gene sequence (Chen and Vasilakis, 2011). DENV-2 is comprised of six genotypes: (i) Asian I representing strains from Thailand, (ii) Asian II representing strains from the Philippines, (iii) Cosmopolitan representing strains from South and South East Asia, (iv) American representing strains from Central America, (v) South East Asian/American representing strains from South East Asia or from Central and South America, and (vi) sylvatic representing strains from West Africa and South East Asia (Chen and Vasilakis, 2011). The Cosmopolitan genotype is composed of two subclades (Chen and Vasilakis, 2011). Subclade (i) was found to be dominated by strains from South Asian countries including India, Sri Lanka, and Bangladesh (Chen and Vasilakis, 2011). This clade originated from a Malaysian strain. Subclade (ii) is distributed worldwide including Africa, South East Asia, the Pacific islands, and Australia. The common ancestor of this clade appeared to originate in Indonesia (Chen and Vasilakis, 2011).

Some epidemiological studies showed that the replacement of the predominantly circulating dengue serotype and/or genotype was associated with increases in the incidence and severity of dengue (Thomas et al., 2008; Vu et al., 2010). In addition, viral evolution is one of the factors conferring higher DENV virulence (Rico-Hesse, 2003). Thus, the geographical movement as well as evolution of DENV need to be considered in order to control dengue infection (Kyle and Harris, 2008; Rico-Hesse, 2003, 2010).

Indonesia is one of the biggest dengue-endemic countries in the world. More than 100,000 cases of DF or DHF are reported annually (Setiati et al., 2006). The first dengue outbreak in Indonesia was reported in Jakarta and Surabaya in 1968 (Hotta et al., 1970; Sumarmo, 1987). Since then, the incidence of dengue has been increasing, with several outbreaks occurring in 1973, 1988, 1998, 2007, and 2010 (Karyanti et al., 2014). All four serotypes of DENV and their genotypes are currently circulating in Indonesia (Suwandono et al., 2006). Even though dengue is considered to be a big problem in Indonesia, molecular epidemiological information on DENV is still limited.

We have continuously isolated DENV in Surabaya, the second biggest city in Indonesia, since 2008. DENV-2 dominantly circulated before October 2008 (Yamanaka et al., 2011). DENV-1 then dominantly circulated between November 2008 and June 2013 with continuous genotype shifts and clade shifts, followed by the predominance of DENV-2 (Kotaki et al., 2014). Thus, sequential changes in the predominant serotype from DENV-2 to DENV-1 and then from DENV-1 to DENV-2 may provide useful information for analyzing the divergence of DENV-2 strains concomitant with serotype shifts.

In the present study, we phylogenetically analyzed DENV-2 isolated in Surabaya between 2008 and 2014 in order to comprehend the viral divergence and evolution of DENV-2 in Indonesia. All DENV-2 strains isolated in Surabaya were classified into Cosmopolitan genotype subclade (ii). These strains shared the most recent common ancestor in 1988, which coincided with the time that an Indonesian dengue outbreak took place. Furthermore, the re-emergence of DENV-2 in Surabaya in 2013–14 may have been due to the loss or decrease of herd immunity or stochastic events rather than viral factors.

2. Materials and methods

2.1. Sample preparation

One hundred ninety nine blood samples were collected from patients diagnosed with dengue at Dr. Soetomo Hospital and Soerya Maternal and Child Health Hospital, major medical facilities covering Surabaya, East Java, Indonesia, with the informed consent of the patients or their parents between January and December 2014. Isolated sera were subjected to virus isolation using Vero cells, as described below. This study was approved by the Ethics Committees of Airlangga University (Ethics Committee Approval Number: 24–934/UN3.14/PPd/2013) and Kobe University Graduate School of Medicine (Ethics Committee Approval Number: 784).

2.2. Virus isolation in cell cultures and RNA extraction

Serum specimens diluted with culture medium (1:10) were inoculated onto a Vero cell monolayer (Yamanaka et al., 2011). The cultures were incubated at 37 °C in 5% CO_2 for seven days. After three blind passages, cells were subjected to immunostaining with a flavivirus group cross-reactive monoclonal antibody (D1–4G2; American Type Culture Collection, Manassas, VA) to examine the presence of viral antigens, as described previously (Konishi et al., 2010). Antigen-positive cells were subjected to RNA extraction using the TRIzol Reagent (Invitrogen, Carlsbad, CA).

2.3. RT-PCR and sequencing

Viral RNA was transcribed to cDNA using the ThermoScript RT-PCR System (Invitrogen, Carlsbad, CA). Types were confirmed following a previous study (Lanciotti et al., 1992), and RT-PCR for the amplification of the E gene was then performed using a type-specific sense primer [5′-CATG GATGTCATCAGAAGGGG-3′; corresponding to nucleotides 764 to 784 of the New Guinea C strain (GenBank accession number AF038403)] and an antisense primer (5′- GCTGACATGAGTTTTGAGTC-3′: nucleotides 2978 to 2959) designed on the prM coding region and the NS protein 1 coding region, respectively. RT-PCR products were purified using illustra ExoProStar (GE Health Care, Little Chalfont, UK) and then directly sequenced using the Big Dye v.1.1 terminator (Applied Biosystems, Foster City, CA). Nucleotide sequences were determined using the ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA).

2.4. Data set of viral isolates used for analyses

Fourteen DENV strains isolated in 2014 in the present study and 568 strains isolated between 2008 and 2013 in our previous studies (Yamanaka et al., 2011; Kotaki et al., 2014) were used for analyzing yearly serotype composition between 2008 and 2014. For sequencing, 42 strains of DENV-2 were randomly selected from 88 strains isolated in Surabaya [13 strains isolated in 2014 in the present study and 75 strains isolated between 2008 and 2013 in our previous studies (Yamanaka et al., 2011; Kotaki et al., 2014)]. Identical sequences were represented by one strain and used for the phylogenetic analysis.

2.5. Phylogenetic analysis

A sequence similarity analysis of the DENV-2 E gene sequence (1485 bp) was performed by Genetyx ver. 10 (Genetyx, Tokyo, Japan). A phylogenetic analysis using the neighbor-joining (NJ) method with a Kimura 2-parameter model was conducted by MEGA5.2 software (Tamura et al., 2011), following previous reports (Rivera-Osorio et al., 2011; Jing et al., 2012).

A total of 2884 DENV-2 E gene sequences were retrieved from the GenBank database for the construction of preliminary phylogenetic tree using NJ method which is suitable for analyzing large amount of

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