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Phylogenetic analysis of dengue virus types 1 and 3 isolated in Jakarta, Indonesia in 1988

Fithriyah Sjatha [a], Yamato Takizawa [b], Atsushi Yamanaka [c], Eiji Konishi [a,b,d,*]

[a] Department of Vaccinology, Center for Infectious Diseases, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
[b] Department of International Health, Kobe University Graduate School of Health Sciences, 7-10-2 Tomogaoka Suma-ku, Kobe, Hyogo 654-0142, Japan
[c] Indonesia-Japan Collaborative Research Center for Emerging and Re-emerging Infectious Diseases, Institute of Tropical Diseases, Airlangga University, Kampus C, Mulyorejo, Surabaya 60115, Indonesia
[d] BIKEN Endowed Department of Dengue Vaccine Development, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchahewi, Bangkok 10440, Thailand[1]

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ABSTRACT

Dengue viruses are mosquito-borne viruses that cause dengue fever and dengue hemorrhagic fever, both of which are globally important diseases. These viruses have evolved in a transmission cycle between human hosts and mosquito vectors in various tropical and subtropical environments. We previously isolated three strains of dengue type 1 virus (DENV1) and 14 strains of dengue type 3 virus (DENV3) during an outbreak of dengue fever and dengue hemorrhagic fever in Jakarta, Indonesia in 1988. Here, we compared the nucleotide sequences of the entire envelope protein-coding region among these strains. The isolates were 97.6–100% identical for DENV1 and 98.8–100% identical for DENV3. All DENV1 isolates were included in two different clades of genotype IV and all DENV3 isolates were included in a single clade of genotype I. For DENV1, three Yap Island strains isolated in 2004 were the only strains closely related to the present isolates; the recently circulated Indonesian strains were in different clades. Molecular clock analyses estimated that ancestors of the genotype IV strains of DENV1 have been indigenous in Indonesia since 1948. We predict that they diverged frequently around 1967 and that their offspring distributed to Southeast Asia, the Western Pacific, and Africa. For DENV3, the clade containing all the present isolates also contained strains isolated from other Indonesian regions and other countries including Malaysia, Singapore, China, and East Timor from 1985–2010. Molecular clock analyses estimated that the common ancestor of the genotype I strains of DENV3 emerged in Indonesia around 1967 and diverged frequently until 1980, and that their offspring distributed mainly in Southeast Asia. The first dengue outbreak in 1968 and subsequent outbreaks in Indonesia might have influenced the divergence and distribution of the DENV1 genotype IV strains and the DENV3 genotype I strains in many countries.

1. Introduction

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are mosquito-borne diseases distributed worldwide. DF is a self-limiting febrile disease, whereas DHF is a fatal disease (WHO, 2012; Halstead, 2007). Since the 1950s, the incidence and geographic distribution of these diseases have dramatically increased (Gubler et al., 2007; Halstead et al., 1997). Currently, 50–100 million patients are estimated annually and more than 2.5 billion people are at risk for these diseases (Wilder-Smith et al., 2010). Thus, DF and DHF are considered one of the major re-emerging infectious diseases of serious global public health concern.

Four genetically related dengue viruses (DENV1–4) exist in nature, which belong to the genus *Flavivirus* of the family *Flaviviridae* (Gubler et al., 2007). Each of DENV1–4 is further divided into genotypes based on nucleotide sequence. Currently, DENV1 comprises five genotypes: (I) Southeast Asia, China, and East Africa; (II) Thailand; (III) Sylvatic (Malaysia); (IV) the Western Pacific islands and Australia; and (V) America, West America, and Asia (Goncalvez et al., 2002; Rico-Hesse, 1990; Chungue et al., 1995). DENV3 also comprises five genotypes: (I) Indonesia, Malaysia, Thailand, the

Abbreviations: DENV, dengue virus; DF, dengue fever; DHF, dengue hemorrhagic fever; E, envelope; NS1, non structural 1; prM, premembrane; BEAST, Bayesian Evolutionary Analysis by Sampling Trees; HPD, highest posterior density; NJ, neighbor-joining.

* Corresponding author at: BIKEN Endowed Department of Dengue Vaccine Development, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchahewi, Bangkok 10440, Thailand. Tel.: +66 2 354 5981; fax: +66 2 255 8377.

E-mail addresses: titi_sjatha@yahoo.com (F. Sjatha), y_takizawa7551@yahoo.co.jp (Y. Takizawa), paradios99@yahoo.co.jp (A. Yamanaka), ekon@biken.osaka-u.ac.jp (E. Konishi).

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South Pacific, the Philippines, and East Timor; (II) Thailand, Myanmar, Singapore, Indonesia, Malaysia, Bangladesh, and Vietnam; (III) Sri Lanka, India, Samoa, Somalia, Japan, Singapore, and Taiwan; (IV) Puerto Rico; and (V) the Philippines and Asia (Messer et al., 2003; Araujo et al., 2009). Phylogenetic studies of DENV1–4 have shown their geographical movement and divergence in particular areas, as well as potential associations between genotypes and disease severity (Kyle and Harris, 2008; Rico-Hesse 2003, 2010).

Indonesia is one of the biggest dengue-endemic countries in the world: in particular, this country has seen the largest incidence of DF and DHF in the Southeast Asian region since 2004 (Suwandono et al., 2006). Metropolitan Jakarta had a high rate of population growth (1.4% in average) from 2000–2010 (Biro Pusat Statistik, 2010). The first dengue outbreak in Indonesia occurred in Jakarta and Surabaya (the second largest city) in 1968, with a total of 58 clinical cases and 24 deaths reported (Sumarmo, 1987). Since then, dengue has been one of the important infectious diseases in Indonesia: dengue outbreak has continued periodically and the disease is currently distributed across the whole Indonesian archipelago (Ong et al., 2008).

Despite its long history of dengue diseases, Indonesia has only limited information on the circulating pathogen: judging by the number of complete envelope gene sequences in GenBank, fewer than 20 strains were isolated before 1990, although more than 100 strains were isolated from 1990 to the present (26th February 2012). Information on the older strains would contribute to an explanation of how this virus has circulated and evolved in Indonesia and other countries. Here, we conducted a molecular epidemiology study using three strains of DENV1 and 14 strains of DENV3, which were isolated during a dengue outbreak in Jakarta, Indonesia in 1988 (Fujita et al., 1997).

2. Materials and methods

2.1. Viruses and cells

Three strains of DENV1 and 14 strains of DENV3 were previously isolated from DF/DHF patients at Cipto Mangunkusmo Hospital in Jakarta, Indonesia in 1988 and were stored at −80 °C at Kobe University School of Medicine, Kobe, Japan. For the present study, the viruses were propagated using the *Aedes albopictus* cell line C6/36. Infected C6/36 cells were maintained for 7 days in Eagle's minimum essential medium supplemented with 10% fetal bovine serum, non-essential amino acids, and 60 μg/ml kanamycin. Because the virus titer was not high enough for viral RNA extraction, the virus was passaged once more through C6/36 cells. The virus was passaged twice through C6/36 cells during the process of isolation in 1988, and the virus used for sequence analysis had been passaged four times through C6/36 cells.

2.2. RNA isolation, reverse transcriptase-polymerase chain reaction (RT-PCR), and sequencing of the envelope (E) protein gene

All viruses were harvested from a 7-days culture of infected C6/36 cells. Viral RNA was extracted from infected culture fluids using TRIzol Reagent (Invitrogen, Carlsbad, CA) and cDNA was produced by RT-PCR using the ThermoScript RT-PCR System (Invitrogen), according to the manufacturer's instructions. Gene-specific antisense primers were designed on the nonstructural 1 (NS1) protein-coding region, while the sense primers were on the premembrane (prM) protein-coding region for each of DENV1 and 3. The PCR product was used for sequencing of the E coding region of each isolate: E is the major surface protein of DENV1–4 and contains a sufficient number of phylogenetically informative sites to distinguish between the genotypes and subtypes of DENV1–4; it is regarded in general as the most appropriate target for phylogeny (Weaver and Vasilakis, 2009).

2.3. Phylogenetic analysis

For homology analysis, we used the Genetyx software (ver.10, Tokyo, Japan). Phylogenetic analysis of the E gene (~1500 nt) was performed using the Bayesian Evolutionary Analysis by Sampling Trees (BEAST) software package v1.5.3 (Drummond and Rambaut, 2007). The year of divergence into each clade was also estimated using a relaxed molecular clock using the Bayesian Markov Chain Monte Carlo method available in BEAST, incorporating information on the virus sampling time. This analysis used a strict molecular clock, a General Time Reversible + Γ_4 model of nucleotide substitution for each codon position, and a Bayesian skyline coalescent model (five-coalescent interval groups); these are the conditions previously reported for DENV analysis (Twiddy et al., 2003; Hang et al., 2010). Similar results, without major differences in topology or coalescence times, were obtained using a relaxed (uncorrelated lognormal) molecular clock and different substitution models. All chains were run for a sufficient length of time (300 million generations) to ensure convergence, with 10% removed as burn-in. This analysis allowed us to estimate times to the most recent common ancestor. The degree of uncertainty in each parameter estimate was provided by the 95% highest posterior density (HPD) value, while the posterior probability values provided an assessment of the degree of support for each node on the tree: in the present study, posterior probability values of $\geqslant 0.9$ were regarded as a significant separation of clades. We also used the neighbor-joining (NJ) method with a Kimura 2-parameter model (Genetyx) to generate a phylogeny.

3. Results

3.1. Nucleotide and amino acid sequences of the E gene

The three DENV1 isolates sequenced in this study had nucleotide identities of 97.6–100%, of which two (D1/JKTA88/88 and D1/JKTA89/88) were completely identical in nucleotide sequence and were represented by D1/JKTA88/88. Thus, two representatives (D1/JKTA4/88 and D1/JKTA88/88) were used for subsequent analyses. Between these two isolates, there were 35 nucleotide differences with two amino acid substitutions. The nucleotide and amino acid identities between the present isolates and the strains belonging to genotype IV of the DENV1 phylogeny were 95.0–99.9% and 98.0–99.8%, respectively.

The 14 DENV3 isolates in this study had nucleotide identities of 98.8–100%, of which four pairs (D3/JKTA15/88 and D3/JKTA18/88, D3/JKTA43/88 and D3/JKTA87/88, D3/JKTA68/88 and D3/JKTA73/88, D3/JKTA99/88 and D3/JKTA101/88) were completely identical. Thus, one of each pair (four isolates) and remaining six isolates were used for subsequent analyses. Among these ten, there were 1–18 nucleotide differences with 1–2 amino acid substitutions. The nucleotide and amino acid identities between the present isolates and the strains belonging to genotype I of the DENV3 phylogeny were 97.0–99.9% and 99.0–100%, respectively.

3.2. Phylogenetic analysis of DENV1 isolated in Indonesia

The two representative DENV1 isolates sequenced in this study were classified into genotype IV, which was defined by Goncalvez et al. (2002): this genotype primarily contains isolates from Australia and the Western Pacific islands. For phylogenetic analysis, we used all the DENV1 strains registered in the GenBank database before February 26th, 2012. From a primary phylogenetic

tree containing more than 1500 strains, strains that were not directly related to the present analysis of the Indonesian isolates were deleted, resulting in the tree shown in Fig. 1: the deletion was done so as not to affect the topology and coalescence times. Despite a large number of deletions, strains that showed nucleotide identities of more than 97%, genotype IV strains of DENV1 that were isolated before 1980, several strains commonly used in a previous report (Yamanaka et al., 2011), and all the fundamental Indonesian strains were retained in this tree. The tree generated by the BEAST analysis was similar to that produced by the NJ analysis.

Overall, the present and previously reported Indonesian isolates (underlined in Fig. 1) were distributed into five clades. Based on a high posterior probability (0.99), the present two isolates were grouped into different clades (clades 1 and 2 in Fig. 1). The D1/JKTA88/88 was close to three strains isolated from Yap Island, Western Pacific, in 2004 (D1/Hu/Yap/31/2004, D1/Hu/Yap/27/

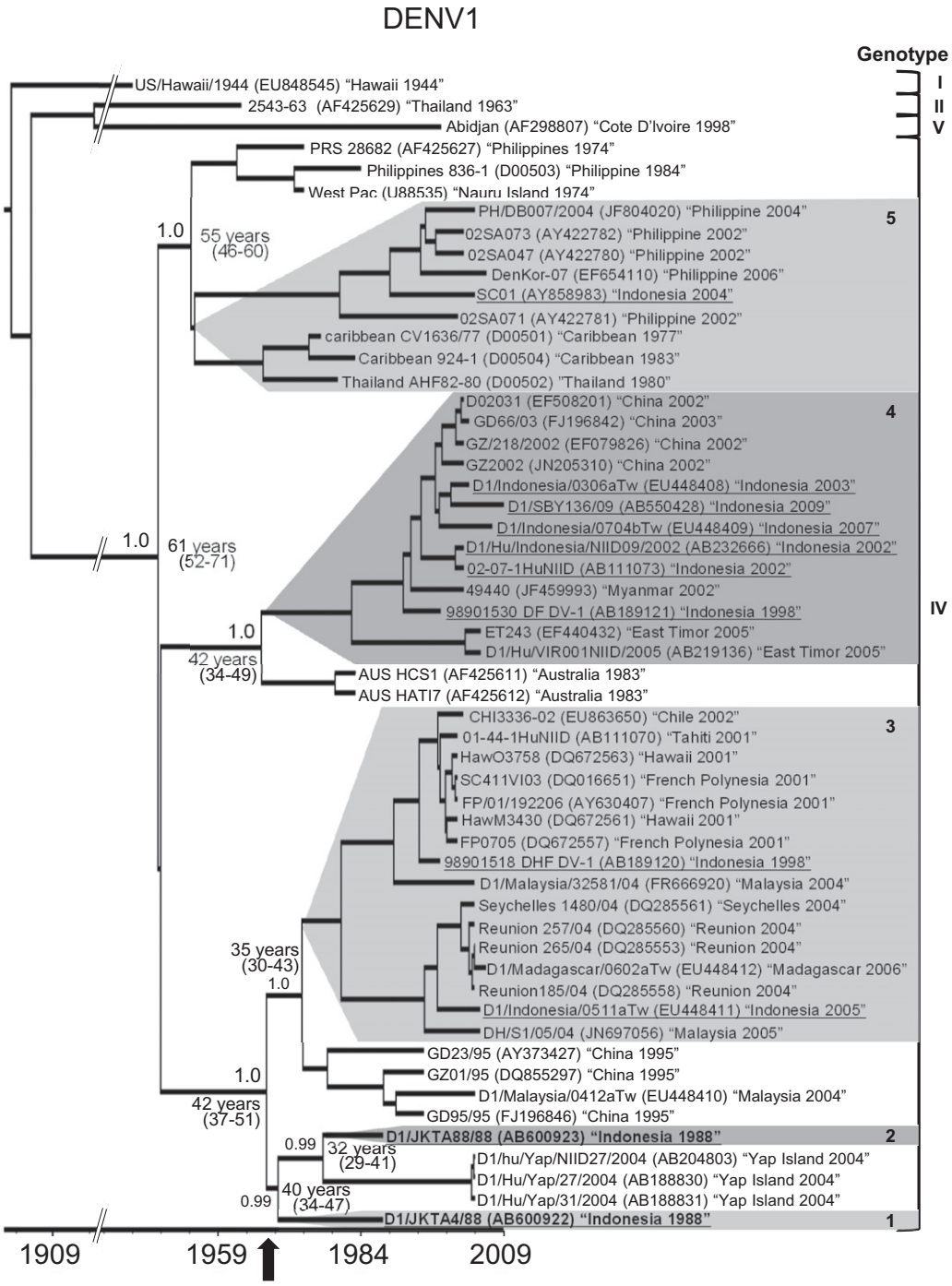

Fig. 1. Maximum clade credibility tree of the E-coding region of DENV1. The GenBank accession number is given in parentheses, followed by the country and year in which the strain was isolated (in quotations). Our isolates are indicated in boldface; Indonesian strains are underlined; clades that include Indonesian strains are enclosed and numbered. Horizontal branches are drawn to scale for the estimated year of divergence with the tip times reflecting the sampling year. The arrow on the horizontal date line indicates the year of the first outbreak in Indonesia. The coalescence times of some key nodes and their 95% HPD values are shown. Posterior probability values $\geqslant 0.9$ are shown above the nodes. The tree is automatically rooted under the assumption of a molecular clock.

2004, and D1/hu/Yap/NIID27/2004) (Nukui et al., 2006). The D1/JKTA88/88 and Yap Island strains were predicted to have the most recent common ancestor, in approximately 1977 (32 years ago based on the isolation year of the most recent strain included in this tree (2009): 95% HPD of 29–41 years). Another Indonesian isolate, D1/JKTA4/88, had no other strains included in the same clade. D1/JKTA4/88 and D1/JKTA88/88 had the most recent common ancestor, which was predicted to have existed in approximately 1969 (40 years ago; 95% HPD of 34–47 years).

Two recent Indonesian strains, 98901518 DHF DV-1 (unpublished) and D1/Indonesia/0511aTw (Shu et al., 2009), were phylogenetically close to our DENV1 isolates, with nucleotide and amino acid identities of 96.5–97.3% and 98.6–99.4% respectively, which were classified into a different clade (clade 3 of Fig. 1) from the present two isolates and shared the most recent common ancestor with the present isolates in approximately 1967 (42 years ago; 95% HPD of 37–51 years). This clade contained strains isolated from a wide area ranging from South America (Chile) through Indonesia, Malaysia and the Western Pacific region (Hawaii and French Polynesia) to the West Indian Ocean (Reunion Island and Madagascar) and Africa (Seychelles). All the other Indonesian strains including the SC01 strain (Ong et al., 2008) and the most recent genotype IV strains of DENV1 reported from Surabaya in 2009 (D1/SBY136/09; Yamanaka et al., 2011) were grouped in other clades (clades 4 and 5) including strains isolated in the Philippines, China, Myanmar, Thailand, East Timor and the Caribbean region. These strains shared the most recent common ancestor with the present isolates in approximately 1948 (61 years ago; 95% HPD of 52–71 years).

3.3. Phylogenetic analysis of DENV3 isolated in Indonesia

All ten DENV3 isolates in this study were classified as genotype I, a genetic lineage that contains strains isolated mainly from Indonesia and the Western Pacific and partly from Malaysia, the Philippines, Taiwan, Thailand, and East Timor (Weaver and Vasilakis, 2009). Similar to the analysis used for DENV1, all the registered DENV3 strains in GenBank were used to construct the first phylogenetic tree, which was later modified by deleting unrelated strains to analyze the present DENV3 isolates: in the process of deletion, the topology and coalescence times were not significantly changed. Also similar to the DENV1 analysis, we used strains available from GenBank with nucleotide identities of more than 97%, genotype I strains of DENV3 that were isolated before 1980, DENV3 strains commonly used in previous studies (Araujo et al., 2009), and all the fundamental Indonesian strains to construct the tree depicted in Fig. 2. The tree generated by BEAST analysis was similar to that produced by NJ analysis.

BEAST analysis of the genotype I strains of DENV3 provided several clades based on posterior probability values of >0.90. All ten isolates were positioned in a single clade (clade 1 of Fig. 2) separated from a clade (clade 2) containing another Indonesian isolate (Indo9108a/Tw) (Huang et al., 2007) with a posterior probability of 0.99. The clade containing the present isolates also contained other Indonesian strains isolated from 1985–2007, as well as strains isolated after 1997 from other countries such as Singapore, China, Malaysia and East Timor. On the other hand, Indonesian strains isolated between 1973 and 1982 (228761, Sleman/78, 1280, and InJ-16-82) (Lanciotti et al., 1994; Blaney et al., 2004) were separated into two different clades (clade 3 and 4) and were also separated from the clade containing our isolates (clade 1) with high posterior probability values of 0.97–1.0. These older strains shared the most recent common ancestor with the present isolates in approximately 1967 and 1970, respectively (43 and 40 years ago based on the isolation year of the most recent strain included in this tree (2010); 95% HPD of 40–48 and 38–44 years, respectively). Strains included in clades 1 and 2 shared the most recent common ancestor in approximately 1980 (30 years ago; 95% HPD of 28–34 years). Thus, common ancestors of these previously reported strains and our isolates were predicted to have evolved frequently between 1967 and 1980.

4. Discussion

The present BEAST analysis of the genotype IV strains of DENV1 indicated that the Indonesian strains were included in five clades. The present isolates, D1/JKTA88/88 and D1/JKTA4/88, were positioned in different clades in the phylogenetic tree (clades 1 and 2 of Fig. 1), and were predicted to have the most recent common ancestor in approximately 1969, suggesting that the two viruses of different clades co-circulated in Indonesia between 1969 and 1988. However, no closely related strains have been isolated from Indonesia since this year, suggesting that these strains were negatively selected in this country. The timing of negative selection is unknown, because no Indonesian strains were registered in GenBank between 1989 and 1998. For strains closely related to D1/JKTA88/88, it is possible that these strains may have circulated in Indonesia for some time period prior to 2004: in 2004, closely related strains were isolated from Yap Island.

The analysis of the genotype IV strains of DENV1 also indicated that a different clade (clade 3 of Fig. 1), containing 98901518/DHFDV-1 and D1/Indonesia/0511aTw, contained strains isolated from several countries in a wide geographic range. In addition, a clade closely related to this clade contained Chinese strains (GZ01/95 and GD95/95) isolated in Guangzhou, Guangdong province in 1995 (Chen et al., 2008; Zheng et al., 2009). Strains contained in these two clades were predicted to have the most recent common ancestor in approximately 1974 and share the most recent common ancestor with the present isolates in approximately 1967. Thus, the first dengue outbreak in 1968 and subsequent outbreaks in Indonesia may be one explanation for the divergence and distribution of the strains in this clade: the increased virus transmission between mosquito vectors and human hosts during the outbreak may have facilitated the virus divergence and distribution through frequent human movement between countries. Consistently, Chinese strains (GZ01/95 and GD95/95) have been proposed to be imported strains from Indonesia (Zheng et al., 2009). In addition, the most recent common ancestor of all previously reported Indonesian strains used in Fig. 1 was predicted to have evolved in approximately 1948, suggesting that the lineage of our isolates and recently circulating strains was indigenous without having caused apparent outbreaks in Indonesia for around 20 years before the first recorded dengue outbreak in 1968.

Analysis of the genotype I strains of DENV3 indicated that all our isolates were included in one clade, which contained previously reported strains isolated within and outside Indonesia between 1997 and 2010, except the 85–159 and den3_88 strains that were isolated in 1985 and 1988, respectively. This suggests that the lineage of our isolates has been continuously circulated in Indonesia and other countries. This clade included strains isolated from Malaysia (MY18-3 and CS81-1) (Holmes et al. 2009) and Indonesia (Indo9909a/Tw, D3/Hu/Indonesia/NIID01/2005, den3_88) (Huang et al., 2007; Ito et al., 2010), which were previously proposed to form the Sumatran-Javan clade, a potential cause of the Indonesian outbreak in 2004 that had unique amino acid substitutions in the E protein (L124S and S301L; Ong et al., 2008). In contrast, some clades containing old Indonesian strains (228761, Sleman/78, 1280, and InJ-16–82) did not contain recently isolated Indonesian strains, suggesting that these strains were negatively selected.

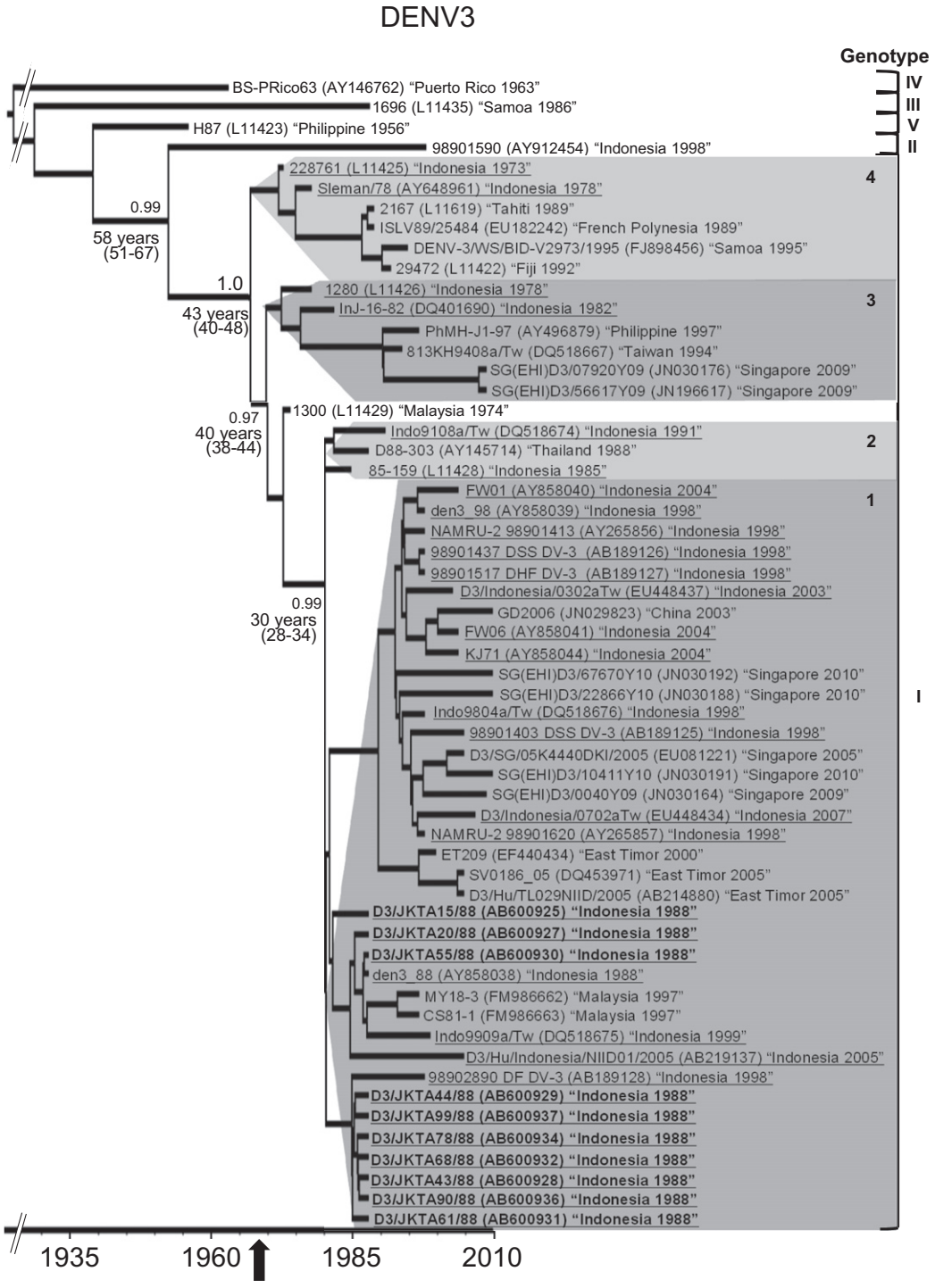

Fig. 2. Maximum clade credibility tree of the E-coding region of DENV3. GenBank accession number, country, and year are shown similarly to Fig. 1. Our isolates are indicated in boldface; Indonesian strains are underlined; clades that include Indonesian isolates are enclosed and numbered. The arrow on the horizontal date line indicates the year of the first outbreak in Indonesia. The coalescence times of some key nodes and their 95% HPD values are shown. Posterior probability values $\geqslant 0.9$ are shown above the nodes. The tree is automatically rooted under the assumption of a molecular clock.

All the previously reported genotype I Indonesian strains of DENV3 were located in several clades that also contained strains isolated from Singapore, Thailand, China, East Timor, Taiwan, the Philippines, and/or French Polynesia. Common ancestors of these Indonesian strains and our isolates were predicted to have diverged frequently between 1967 and 1980. In contrast to the genotype IV strains of DENV1, the first genotype I strain of DENV3 emerged in approximately 1967: based on the most ancestral strain (Indonesian 228761) and the wide inclusion of Indonesian strains in many DENV3 genotype I clades, the first probably appeared in Indonesia. However, similar to the genotype IV strains of DENV1, dengue outbreaks in Indonesia starting in 1968 may have caused divergence of the DENV3 genotype I virus, which affected the viral circulation and evolution within and outside Indonesia.

In conclusion, the addition of old Indonesian isolates to our phylogenetic analysis considerably increased our knowledge of the

evolution of genotype IV strains of DENV1 and genotype I strains of DENV3. For both DENV1 and DENV3, the first outbreak in 1968 and subsequent outbreaks in Indonesia may have caused the frequent divergence of viral strains, which were better adapted to grow in the transmission cycle between humans and mosquitoes in a particular environment. Using the Indonesian DENV1 and DENV3 strains, we were able to propose repeated positive and negative selection of the newly diverged viral strains in Indonesia and the distribution of these strains to other countries.

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