

THE MOLECULAR EPIDEMIOLOGY OF FOUR SEROTYPES OF DENGUE VIRUSES CIRCULATING IN THAILAND DURING 1974 TO 2001

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Dengue represents a major public health problem in Thailand, with all four viral serotypes co-circulating. This provides an optimal setting to investigate the molecular epidemiological history and evolutionary trends of these co-circulating dengue virus (DENV) serotypes in a highly endemic country; to characterize intra-serotypic variations of DENV in a locality; to determine the evolutionary forces shaping viral genetic diversity; to determine whether the changing prevalence of DENV could be attributed to instances of adaptive evolution in the viral genome. Furthermore, it permits the investigations of whether molecular determinants of the envelope (E) gene of DENV correlate with disease severity. To this end, we undertook a large-scale molecular epidemiological analysis of 324 E gene sequences of DENV representing each of the 4 serotypes (98 DENV-1, 105 DENV-2, 68 DENV-3 and 53 DENV-4) and 32 complete genome sequences of DEN viruses (10 DENV-1, 10 DENV-2, 6 DENV-3 and 6 DENV-4) isolated from children admitted from 1974 to 2001 in Thailand (Bangkok and Kamphaeng Phet) with varying degrees of dengue severity [dengue fever/dengue hemorrhagic fever/dengue shock syndrome (DF/DHF/DSS)]. Our results indicated that there was no obvious molecular correlate between disease severity and the phylogenetic position of their associated E genes. These analyses revealed extensive genetic diversity within a single geographic locality at a single time, including the discovery of a new and divergent genotype of DENV-4. However, despite this abundant genetic variation, there was no evidence of adaptive evolution in any gene, codon, or lineage of DENV-3 and DENV-4 (DENV-1 and DENV-2 analyses are ongoing.) The phylogenetic trees of DENV showed a strong temporal structure, ladder-like structure for all 4 serotypes; viral strains isolated at the earliest time-points tended to fall near the root of the trees, while those sampled more recently were located more remote from the root of the trees. These temporal orderings are caused by the continual birth and death of viral lineages; new lineages are regularly produced by mutation, but most go extinct relatively rapidly and few progress to circulate in subsequent years. Consequently, the rapid turnover of DENV lineages observed is, at most, the consequence of high rates of deleterious mutations in the viral genome coupled with seasonal fluctuations in the size of the vector population.

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MOLECULAR EVOLUTION AND EPIDEMIOLOGY OF DEN –4 VIRUSES IN BANGKOK, THAILAND

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Fifty-three dengue-4 (DEN-4) virus isolates from children in Bangkok, admitted with varying severity of DEN [dengue fever/dengue hemorrhagic fever/dengue shock syndrome (DF/DHF/DSS)]