Molecular Epidemiology of Human Enterovirus 71 Strains and Recent Outbreaks in the Asia-Pacific Region: Comparative Analysis of the VP1 and VP4 Genes

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This study provides a comprehensive overview of the molecular epidemiology of human enterovirus 71 (HEV71) in the Asia-Pacific region from 1997 through 2002. Phylogenetic analysis of the VP4 and VP1 genes of recent HEV71 strains indicates that several genogroups of the virus have been circulating in the Asia-Pacific region since 1997. The first of these recent outbreaks, described in Sarawak (Malaysian Borneo) in 1997, was caused by genogroup B3. This outbreak was followed by large outbreaks in Taiwan in 1998, caused by genogroup C2, and in Perth (Western Australia) in 1999, where viruses belonging to genogroups B3 and C2 cocirculated. Singapore, Taiwan, and Sarawak had HEV71 epidemics in 2000, caused predominantly by viruses belonging to genogroup B4; however, large numbers of fatalities were observed only in Taiwan. HEV71 was identified during an epidemic of hand, foot and mouth disease in Korea; that epidemic was found to be due to viruses constituting a new genogroup, C3.

Human enterovirus 71 (HEV71) was first isolated in 1969 (1) and is most often associated with outbreaks of the mild childhood exanthem, hand, foot and mouth disease (HFMD) (2). HEV71 is closely related to coxsackie virus A16 (CA16), the other major causative agent of HFMD, but unlike CA16, HEV71 is also associated with cases of acute neurologic disease including poliomyelitis-like paralysis, encephalitis, and aseptic meningitis (3,4). Although HEV71 outbreaks associated with small numbers of cases of severe neurologic disease were reported in the 1980s in Australia (5), Asia (6), and the United States (4), mortality associated with such outbreaks was low, unlike earlier outbreaks in Bulgaria in 1975 (7) and Hungary in 1978 (8). Twenty years later in 1997, deaths associated with epidemics of HEV71-associated HFMD in Sarawak, Malaysia (9), followed closely by outbreaks with high mortality in Taiwan in 1998 and 2000 (10,11), have raised considerable public concern about the virulence of this virus and the disease syndromes most recently attributed to it (12–14).

Several groups have attempted to describe the molecular epidemiology of HEV71 in the Asia-Pacific region, and the phylogenetic relationships of recent HEV71 strains to earlier strains from Asia and other parts of the world have been described (15–19). In the past 4 years, nine publications have presented comparative analyses of HEV71 strains based on several genome regions (Table 1). Taken together, more than 250 HEV71 strains isolated from the region between 1997 and 2002 have been analyzed by different groups. However, gaining a comprehensive insight into the phylogenetic relationships between all these HEV71 strains has been difficult because of the lack of a standardized methodology. The strategies used by each of these groups are summarized in Table 1.

We sequenced the complete VP1 gene of 66 HEV71 isolates from Singapore, Sarawak (Malaysian Borneo), and Perth, Western Australia, from 1997 to early 2001 (22) and determined that these recent strains were from the genogroups B and C, based on the nomenclature of Brown et al. (21). In Sarawak in 1997, isolates from fatal and nonfatal cases all belonged to genogroup B, in a previously undescribed cluster that we have named B3 (22). Viruses belonging to genogroup B3 were also isolated in Singapore in 1998, and B3 was the genogroup most commonly identified for viruses isolated in Perth during 1999. However, HEV71 strains isolated from children with severe neurologic disease during the Perth epidemic belonged to genogroup C2 (22). Another previously undescribed genogroup B cluster (B4) was identified in Singapore in 1997 and continued to circulate there in 2000 (23) through 2002. Viruses from genogroup B4 were also identified as the primary cause of a large HFMD outbreak in Sarawak in 2000.

As several regions of the HEV71 genome have been used in phylogenetic studies, including the VP1 (21,22) and VP4 (15,19) genes and the 5′ untranslated region (5′ UTR) (16,20),

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