Evolutionary Genetics of Human Enterovirus 71: Origin, Population Dynamics, Natural Selection, and Seasonal Periodicity of the VP1 Gene
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Human enterovirus 71 (EV-71) is one of the major etiologic causes of hand, foot, and mouth disease (HFMD) among young children worldwide, with fatal instances of neurological complications becoming increasingly common. Global VP1 capsid sequences (n = 625) sampled over a decade were collected and subjected to comprehensive evolutionary analysis using a suite of phylogenetic and population genetic methods. We estimated that the common ancestor of human EV-71 likely emerged around 1941 (95% confidence interval [CI]; 1929 to 1953), subsequently diverging into three genogroups B, C, and the now extinct genogroup A. Genealogical analysis revealed that diverse lineages of genogroup B and C (subgenogroups B1 to B3 and C1 to C5) have each circulated explicitly in the human population for up to 5 years before causing large HFMD outbreaks, indicating the quiescent persistence of EV-71 in human populations. Estimated phylodynamic showed a complex pattern of spatial structure within well-sampled subgenogroups, suggesting endemism with occasional lineage migration among locations, such that most HFMD epidemics are unlikely to be linked to continuous transmission of a single strain of virus. In addition, large genetic variants are correlated with the onset of epidemics, driven in part by the emergence of novel EV-71 subgenogroups. Using subgenogroup C1, as a model, we observe temporal strain replacement through time, and we investigate the evidence for positive selection at VP1 immunogenic sites. We discuss the consequences of the evolutionary dynamics of EV-71 for vaccine design and compare its phylodynamic behavior with that of influenza virus.

Enterovirus 71 (EV-71) is a member of the genus Enterovirus in the family Picornaviridae. Classified as human enterovirus species A (HEV-A), EV-71 is a small, nonenveloped, positive-stranded RNA virus with a genome approximately 7.4 kbp long and is genetically most related to CV-A16. EV-71 is divided into three major genogroups (genogroup A, B, and C), and various subgenogroups within genogroups B and C.

Since its first isolation in the United States in 1969 (71), EV-71 has been identified worldwide as a common cause of hand, foot, and mouth disease (HFMD) in young children and infants. Large EV-71-associated HFMD outbreaks have been reported in the United States, Europe, Australia, and Asia and constitute a significant and emerging threat to global public health (6, 56, 62, 63). Although EV-71 infection manifests most frequently as a mild, self-limited febrile illness characterized by papulovesicular lesions on the hands, feet, and oral mucosa, and in humans, a small proportion of acute infections are associated with fatal neurological symptoms, including brain stem encephalitis, encephalitis lethargica, and poliomyelitis-like paralysis (4, 24, 28). In such cases, meningitis and cerebral hemorrhage are also common. In Malaysia in 2005 (2, 13, 16, 43) and Taiwan in 1998 (34, 42), smaller outbreaks occurred with high case fatality rates. The first reported in 1978 (21) and Hong Kong in 1978 (62). Although large HFMD epidemics with high mortality rates occurred 2 decades later, in Malaysia in 2005 (2, 13, 16, 43) and Taiwan in 1998 (34, 42), following these outbreaks, the Asia-Pacific region has experienced more frequent large-scale EV-71-associated HFMD epidemics with a high incidence of neurological infections and significant case fatality rates— and the virus has attracted global attention (5, 34, 15, 64, 37, 46, 48, 55, 57, 74, 81, 92). Intriguingly, almost all outbreaks reported in the Asia-Pacific region during the last decade were caused by previously