Millions of incidents of hand, foot and mouth disease occur annually in China, with EVA71 and CVA16 as two major causative pathogens. A provincial surveillance system has been implemented in Guangdong for almost 5 years to analyze the aetiological spectrum and epidemic changes. An unusual enterovirus type, CVA6, was identified as the predominant serotype associated with an HFMD epidemic from late 2012 to 2013. In contrast to virus strains isolated before, all CVA6/CHN/2012–2013 strains segregated into one major genetic cluster. This study suggested that one cluster of circulating CVA6 strain had emerged as a new and major cause during a continuing HFMD epidemic in Guangdong, China.