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Molecular epidemiology and genetic history of European-type genotype 3 hepatitis E virus indigenized in the central region of Japan [☆]

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ABSTRACT

In Mie prefecture in Japan, 12 cases of sporadic hepatitis E occurred from 2004 to 2011. Mie prefecture is located in the central region of Japan, far from the most prevalent regions of hepatitis E virus (HEV) infection in Japan, the north and northeastern part. These 12 cases did not have any common risk factors of HEV infection. We analyzed the molecular epidemiology of the cases in Mie prefecture. We obtained the nucleotide sequences of the HEV strains and analyzed them with the sequences of other HEV strains by phylogenetic and coalescent analyses. Japan-indigenous genotype 3 HEV strains were divided into two major subtypes, namely, 3a and 3b; one minor subtype, 3e; and a few other unassigned lineages. The Japan-indigenous subtype 3e strains were closely related to European subtype 3e HEV strains and were comparatively rare in Japan; however, eight strains of the 12 cases we examined belonged to subtype 3e, indicating a close phylogenetic relationship, despite the lack of common risk factors. Coalescent analyses indicated that the Mie 3e strains seemed to have intruded into Mie prefecture about 10 years ago. Sporadic acute hepatitis E cases caused by the 3e strains occurred consistently from 2004 to 2011 in Mie prefecture. This is the first report of unexpected persistent occurrence of hepatitis by the European-type genotype 3 HEV, subtype 3e, in a country outside of Europe. Phylogenetic and coalescent analyses traced the history of the indigenization of the Mie 3e strains from Europe. Because hepatitis E cases caused by 3e strains are relatively rare in Japan, molecular evolutionary analyses of HEV infection in Mie prefecture is important for preventing a future hepatitis endemic or epidemic by 3e strains in Japan.

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Abbreviations: BSP, Bayesian skyline plot; MCMC, Markov chain Monte Carlo; BF, Bayes factor; TMRCA, time of the most recent common ancestor.

[☆] The GenBank/EMBL/DDBJ accession numbers of new genotype 3 HEV sequences determined in this study are AB607887, AB607889, AB607891, AB607892, AB607893, AB670119, AB670120, AB670123, and AB670124.

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1. Introduction

Hepatitis E virus (HEV) is a positive-sense, single-stranded RNA virus consisting of approximately 7200 nt. It is a member of the genus *Hepevirus* in the *Hepeviridae* family (Emerson et al., 2005). The genome contains three open reading frames (ORFs), namely, ORF1, ORF2, and ORF3 (Chandra et al., 2008; Emerson et al., 2010; Yamada et al., 2009). HEV is the causative agent of hepatitis E. Outbreaks of hepatitis E generally occur in developing countries,

where water sources are sometimes contaminated by feces containing HEV (Bradly et al., 1993; Okamoto, 2007); however, sporadic cases of hepatitis E have been reported in industrialized countries as well. Evidence from Japan and Europe have shown that HEV can be zoonotically transmitted to humans through the consumption of meat or offal of swine, wild boar, and deer infected with HEV (Bouwknegt et al., 2007; Reuter et al., 2009; Tamada et al., 2004; Tei et al., 2004; Yazaki et al., 2003).

Global HEV strains have been segregated into four genotypes, numbered 1–4 (Schlauder and Mushahwar, 2001). Lu et al. proposed further subtyping of each genotype through phylogenetic analyses (Lu et al., 2006). Recently, candidates for new genotypes were reported from rats (Johns et al., 2010) and rabbits in China (Zhao et al., 2009), and wild boars in Japan (Takahashi et al., 2010a, 2011). Genotypes 1 and 2 infect only humans and are associated with hepatitis E outbreaks in developing countries (Bradly et al., 1993; Okamoto, 2007), whereas genotype 3 strains have been isolated all over the world (Kaba et al., 2010; Lu et al., 2006), and genotype 4 cases have been reported in Asia, mainly in Japan and China (Lu et al., 2006). In a report involving 254 cases of Japanese hepatitis E cases, most of the cases were sporadic cases by genotypes 3 and 4 (Abe et al., 2006), and water-borne outbreaks by genotype 1 or 2 have not been reported in Japan. The etiology of hepatitis E caused by genotypes 3 and 4 can be complex. In the above-mentioned study in Japan (Abe et al., 2006), some cases were caused by the ingestion of food products from pigs, boars, and deer infected with genotype 3 or 4 HEV strains. However, ~60% of the cases had no clear risk factors (i.e., travel to endemic

area, transfusion, eating uncooked or undercooked mammalian liver or colon) for HEV infection, and the etiology remains to be determined. In addition, the contributions that the newly discovered genotypes are making to human disease are also unknown.

A nationwide survey revealed that genotype 3 is the most prevalent HEV genotype infecting humans (Sakata et al., 2008; Takahashi et al., 2010b) and swine (Takahashi et al., 2003) in Japan. Mizuo et al. first reported that multiple lineages of HEV genotype 3 are co-circulating in Japan, and these contribute to the development of sporadic acute hepatitis, with the prevalence differing according to age, sex, and geographic region (Mizuo et al., 2002). In our previous study, we reported that Japan-indigenous genotype 3 HEV was divided into at least three lineages, and that the European strains also originated from several lineages (Nakano et al., 2012).

Since November 2003, doctors in Japan are required to report all cases of hepatitis E to the local health bureau. The details of all reported cases can be found at the National Infectious Disease Surveillance Center in Japan (<http://idsc.nih.go.jp/index-j.html>). Around 41–71 cases have been reported in Japan every year from 2004 to 2011. Japan consists of four major islands: Hokkaido, Honshu (the main island), Shikoku, and Kyushu, situated from northeast to southwest (Fig. 1a). Mie prefecture is located in central region of the Honshu (Fig. 1a), far from the most prevalent regions of hepatitis E infection in Japan, which occur in the northeastern part of Honshu and in Hokkaido (Abe et al., 2006; Inoue et al., 2009b; Sainokami et al., 2004). In Mie prefecture, 0–4 cases of hepatitis E were reported annually, and a total of 16 cases have been reported from 2003 to 2011. We obtained serum samples from

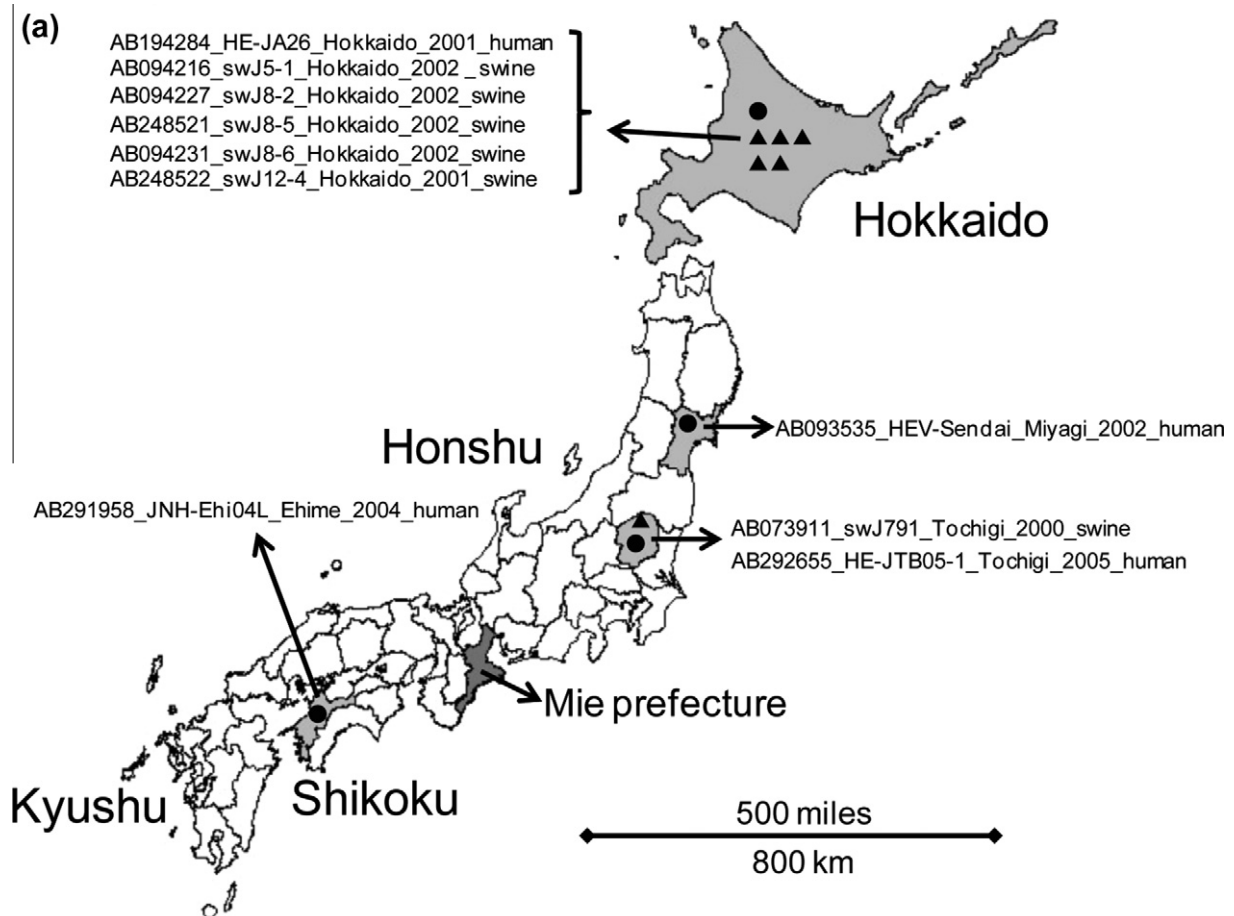


Fig. 1a. Map showing the four major islands of Japan, namely, Hokkaido, Honshu, Shikoku, and Kyushu, and the 47 prefectures. Gray indicates prefectures where the European-type genotype 3 HEV 3e strains were isolated. Black circles and triangles indicate strains isolated from human and swine, respectively. Accession numbers, strains, prefectures, years of isolation, and hosts are indicated at the tip of each arrow. Mie prefecture, which is investigated in this study, is indicated, with the details in Fig. 1b.

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