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LETTER TO THE EDITOR

HCC-Associated Viral Mutations in Patients with HBV Genotype F1b Infection

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Hepatitis B virus (HBV) infection is a serious risk factor for development of hepatocellular carcinoma (HCC). The distribution of HBV genotypes varies geographically and ten genotypes of HBV have been identified and labelled A-J. HBV single nucleotide variants (SNVs) have been determined to be associated with hepatocarcinogenesis [1,2]. However, most of the studies have focused on genotypes B and C. Other genotype-oriented inclinations which develop certain HCC-associated viral mutations are yet largely unknown.

Recently, a study by Hayashi et al. [3] demonstrated that core T1938C (V13A) and A2051C (N51H) mutations had accumulated together with A1762T/G1764A mutations in the basal core promoter (BCP) region and the G1896A mutation in the pre-core region (PC) in HCC patients with HBV genotype F1b infection, suggesting a functional association between these variants and hepatocarcinogenesis in Alaska Native (AN) people [3,4]. This study significantly advances our understanding of the role of HBV variants in the pathogenesis of HCC. However, several points still need further investigation.

First, are these core mutations Alaska specific? Genotype F is one of the less-studied genotypes with four subgenotypes (F1 to F4), predominantly found in the native populations of Alaska, Central America, and South America. It has also been detected sporadically worldwide [5]. With this background in mind, 105 HBV F1b full-length genomic sequences were retrieved from

Table 1. HBV F1b full-length genomic sequences retrieved from GenBank.

Country	Accession	Genotype
Argentina	AF223963 AF223964 AY179735 DQ823091 DQ823092 DQ823093 DQ823094 DQ823095 EU366118 EU366133 FJ657525 FJ657529 HE981182 HE981183 JN688691 JN688699 JN688703 JX079936 KJ843163 KJ843164 KJ843167 KJ843168 KJ843169 KJ843170 KJ843171 KJ843174 KJ843176 KJ843177 KJ843178 KJ843179 KJ843180 KJ843181 KJ843190 KJ843193 KJ843194 KJ843195 KJ843196 KJ843197 KJ843198 KJ843199 KJ843200 KJ843201 KJ843202 KJ843203 KJ843204 KJ843205 KJ843206 KY382415	F1b
Brazil	KC494400 KC494404	F1b
Chile	FJ709457 FJ709458 FJ709459 FJ709460 FJ709462 FJ709463 FJ709464 FJ709465 FJ709494 HM585186 HM585187 HM585188 HM585189 HM585190 HM585191 HM585192 HM585193 HM585194 HM585195 HM585196 HM585197 HM585198 HM585199 HM585200 HM590471 HM590472 HM590473 HM590474 HM622135 HM627320 KM233681 KX264496	F1b
Japan	AB086397 AB116654	F1b
Mexico	KF199901 KM998715 KY458061 KY458062	F1b
Peru	EU670261 EU670262	F1b
Uruguay	KJ586805 KJ586806 KJ586807 KJ586808	F1b
Venezuela	AB116552 KP995098 KP995116	F1b
USA: Alaska	JN792914 JN792916 JN792917 JN792918 JN792919 JN792920 JN792921 JN792922	F1b

GenBank (Table 1). In addition to some mentioned in the study of Hayashi et al. [3], including Argentina, Chile, Peru, Venezuela, and Alaska, those derived from Brazil, Mexico, Uruguay, and Japan were also investigated in this study. A phylogenetic tree was constructed by the neighbor joining method (Figure 1A). Similar to the report by Hayashi et al. [3], neither T1938C nor A2051C mutation was identified in Brazil, Mexico, Peru, Uruguay or Venezuela. However, these core mutations were unexpectedly found in Argentina, Chile, and Japan (Figure 1B). Whether these variants are also associated with HCC risk in HBV F1b patients from other regions and ethnic groups warrants further study.

Second, are there any other mutations specific to Alaska? To address this question, complete HBV genome analysis was performed in all the strains. Interestingly, the T3102C mutation was uniquely identified in genotype F1b of Alaska but not of any others (Figure 1C). T3102C mutation would result in tyrosine to histidine substitution in HBV polymerase. Furthermore, the T3102C mutation occurred in the SPII promoter region, which was essential for the transcription of HBV 2.1-kb subgenomic RNA and the subsequent M/S protein and HBsAg production. It would be of great interest to study whether this mutation might contribute independently or jointly to the oncogenesis of HCC in individuals with HBV F1b infection.

Overall, these further explorations will deepen our insights into the role of viral mutations in hepatocarcinogenesis and will be favorable for personalized programs of surveillance and treatment for patients with HBV infection.

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Declaration of Interest:
There are no conflicts of interest.

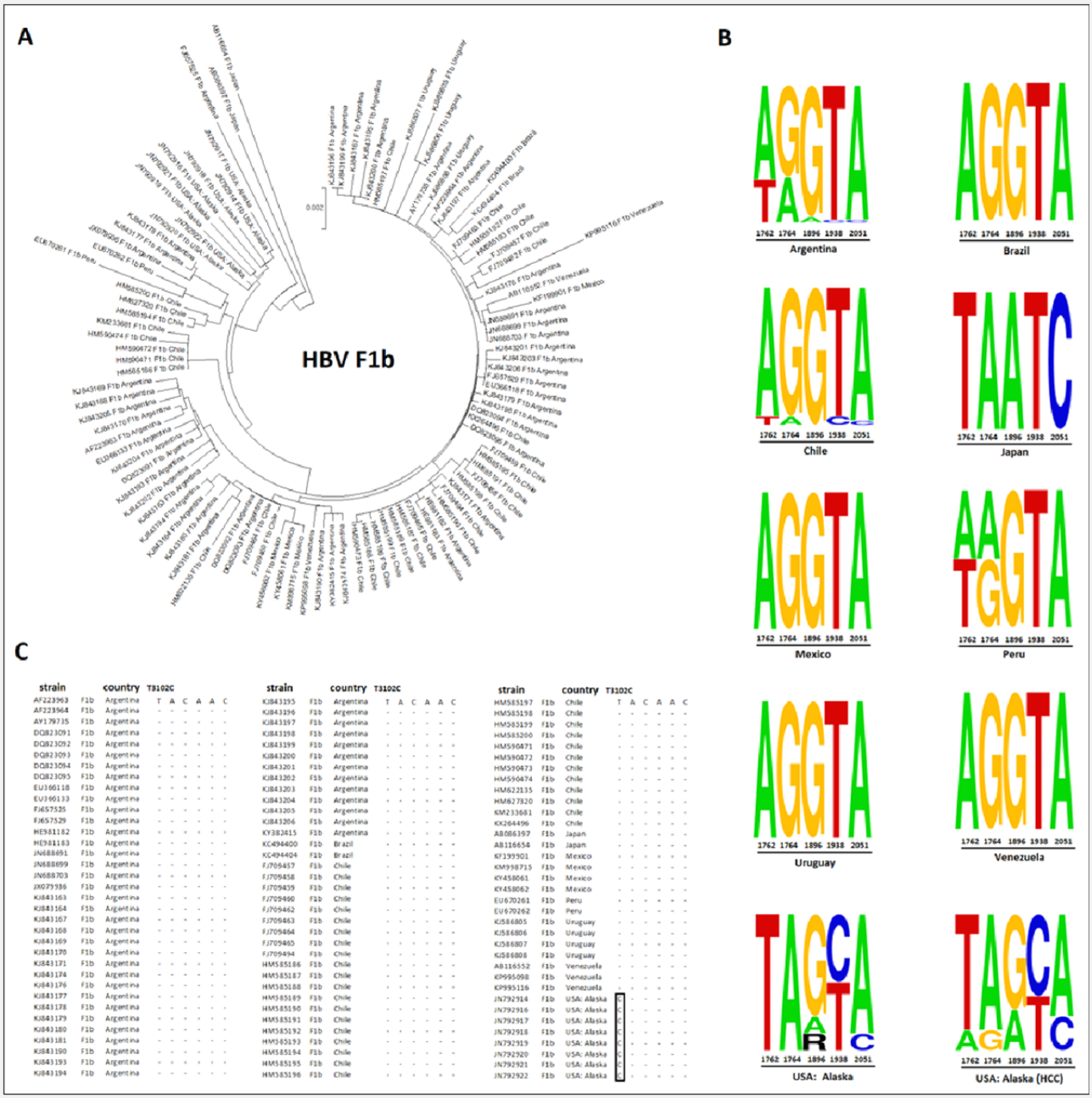

Figure 1. HCC-associated viral mutations in patients with HBV genotype F1b infection.

(A) Phylogenetic tree was constructed by the neighbor joining method, based on the full-length genomic sequences of HBV F1b strains. Accession numbers and locations were shown in each branch. (B) Graphical representation of alignment of nucleotide sequences of HBV F1b strains using weblogo in positions 1896, 1762, 1764, 1938 and 2051, respectively. The height of symbols indicates the relative frequency of nucleic acid at that position. (C) Alignment of nucleotide sequences of HBV F1b strains. The T3102C mutation uniquely in genotype F1b of Alaska was boxed.

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