Hepatitis B virus (HBV), because of its error-prone viral polymerase, has a high mutation rate leading to widespread substitutions, deletions, and insertions in the HBV genome. Deletions may significantly change viral biological features complicating the progression of liver diseases. However, the clinical conditions correlating to the accumulation of deleted mutants remain unclear. In this study, we explored HBV deletion patterns and their association with disease status and antiviral treatment by performing whole genome sequencing on samples from 51 hepatitis B patients and by monitoring changes in deletion variants during treatment. Clone sequencing was used to analyze preS regions in another cohort of 52 patients. Among the core, preS, and basic core promoter (BCP) deletion hotspots, we identified preS to have the highest frequency and the most complex deletion pattern using whole genome sequencing. Further clone sequencing analysis on preS identified 70 deletions which were classified into 4 types, the most common being preS2. Also, in contrast to the core and BCP regions, most preS deletions were in-frame. Most deletions interrupted viral surface epitopes, and are possibly involved in evading immuno-surveillance. Among various clinical factors examined, logistic regression showed that antiviral medication affected the accumulation of deletion mutants (OR = 6.81, 95%
CI = 1.296 – 35.817, P = 0.023). In chronic carriers of the virus, and individuals with chronic hepatitis, the deletion rate was significantly higher in the antiviral treatment group (Fisher exact test, P = 0.007). Particularly, preS2 deletions were associated with the usage of nucleos(t)ide analog therapy (Fisher exact test, P = 0.023). Dynamic increases in preS1 or preS2 deletions were also observed in quasispecies from samples taken from patients before and after three months of ADV therapy. In vitro experiments demonstrated that preS2 deletions alone were not responsible for antiviral resistance, implying the coordination between wild type and mutant strains during viral survival and disease development. We present the HBV deletion distribution patterns and preS deletion substructures in viral genomes that are prevalent in northern China. The accumulation of preS deletion mutants during nucleos(t)ide analog therapy may be due to viral escape from host immuno-surveillance.

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