

Occult hepatitis B virus infection in chronic liver disease: full-length genome and analysis of mutant surface promoter

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Abstract:

BACKGROUND AND AIMS: Genome sequence of hepatitis B virus (HBV) from occult chronic infection is scarce. Fifty-six (9.4%) of 591 patients seronegative for hepatitis B surface antigen (HBsAg) with chronic liver disease were positive for HBV DNA. The complete HBV genome from 9 of these patients (S1-S9) and 5 controls positive for HBsAg (SWT.1-SWT.5) were analyzed. **METHODS:** Overlapping genome fragment amplification, cloning, and sequencing was performed on these cases. Functional analysis of surface promoter was conducted using fusion construct. **RESULTS:** All patients with occult infection except one (S8) had a low viral titer. Eight patients had infection with genotype A (S1-S5, SWT.1-2, SWT.5) and 6 had infection with genotype D (S6-S9, SWT.3-4). S4 and S5.1 of genotype A had the characteristic nucleotide deletions in core and pre-S1 region seen in genotype D. The major observations in patients with occult HBV infection were as follows: frequent quasispecies variation, deletions in pre-S2/S region affecting the surface promoters (nt 3025-54) and pre-S protein (S3, S5, S6, S8), truncated precore (S6, S8, S7.1) and core (S9) owing to stop signal, alternate start codon for the Polymerase gene (S3, S9), and YMDD mutation (S1, S4, S9) in patients not on antiviral therapy. HBsAg and core proteins could be shown immunohistochemically in 3 of 5 liver biopsy specimens available. The mutant surface promoters (pre-S2 and S) on functional analysis showed alterations in HBsAg expression. **CONCLUSIONS:** These changes in the regulatory region with possible alterations in the ratio of large and small surface proteins along with other mutations in the genome may decrease the circulating HBsAg level synergistically, making the immunodetection in serum negative.