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Evolutionary and molecular aspects of surface antigen (HBsAg) gene mutants in blood donors with occult Hepatitis B virus infection

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We sequenced 203 nucleotides (position 457-659 in the genome), in the region of the HBsAg "a determinant" from 233 isolates of HBV, genotype D/*ayw*. Samples were collected from 36 HBsAg/HBcAg-negative blood donors (years 2007-2009, PROCLEIX® ULTRIO® Assay, Novartis). The experimental plan was designed to test whether the escape mechanism of occult mutants was based on misfolding in the HBsAg region.

After selection of 105 non-redundant mutants, a Maximum Likelihood (ML) phylogenetic analysis yielded a tree with four clusters supported by high bootstrap values, documenting the existence of at least four important HBV variants. The analysis at the Datamonkey server (www.datamonkey.org) identified a breakpoint centered on position 569 (codon 138 in the HBsAg-coding sequence), with an averaged confidence for recombination higher than 99%, and both branches and sites evolving under positive selection ($p<0.05$).

Because of the lack of a crystallography-resolved reference structure of the HBsAg protein, we obtained in silico the "*ab initio*" tertiary structures (http://zhanglab.ccmb.med.umich.edu/I-TASSER) in a subset of sequences, selected from each cluster of the phylogenetic tree and/or expressing rare mutations (e.g. insert/deletion and precocious stop codons). To these structures we superimposed the conformational epitopes identified by the ELLIpro at the IEDB server (http://immuneepitope.org/): the comparison of results put into striking evidence the severe disruption of the wild-type epitopes. The docking with human antibodies (ClusPro at http://nrc.bu.edu/cluster/) was only partially conserved.

Our data support the hypothesis that the lack of reactivity with the most sensitive HBsAg assays could be due to an antigenic impairment consequent to misfolding.

Biography

Anna Giulia Cattaneo has completed her M.D. at the age of 25 years (Nov 3, 1977) from the University of Milano, Italy, and a post-graduation stage at Karolinska Institutet, Sweden. Since then, she has worked mainly for academic research, in the fields of bioinformatics, metabolism and experimental medicine. She is co-author of more than 20 papers on peer-reviewed journals and some chapters of books. She participated as an active member to several international Congresses/Symposia. She is a member of the N.Y. Academy of Sciences.