

**Table S1. Predicted proteins from HBV encoded reading frames based on reliability of AUG initiation codons<sup>1</sup>.**

| mRNA <sup>2</sup> | Viral protein <sup>3</sup>    | Identity to A/GXXATGG | Reliability <sup>4</sup> | ORF length (Aa) | Predicted molecular weight (kDa) | Sequence <sup>5</sup>  |
|-------------------|-------------------------------|-----------------------|--------------------------|-----------------|----------------------------------|--|
| pg RNA            | <b>canonical core protein</b> | GXXATGG               | 0.36                     | 183             | 21                               | H <sub>2</sub> N- <b>M1</b> -X64- <b>M2</b> -X26- <b>M3</b> -X90-COOH                  |
|                   | core isoform 1                | tXXATGa               | 0.11                     | 118             | 13.6                             | H <sub>2</sub> N- <b>M2</b> -X26- <b>M3</b> -X90-COOH                                  |
|                   | core isoform 2                | AXXATGG               | 0.07                     | 91              | 10.6                             | H <sub>2</sub> N- <b>M3</b> -X90-COOH  |
| pg RNA            | <b>canonical P protein</b>    | cXXATGc               | 0.91                     | 843             | 94.2                             | H <sub>2</sub> N- <b>M1</b> -X473- <b>M2</b> -X179- <b>M3</b> -X188-COOH               |
|                   | P protein isoform 1           | AXXATGc               | 0.31                     | 369             | 41                               | H <sub>2</sub> N- <b>M2</b> -X179- <b>M3</b> -X188-COOH                                |
|                   | P protein isoform 2           | cXXATGc               | 0.29                     | 189             | 20.8                             | H <sub>2</sub> N- <b>M3</b> -X188-COOH   |
| preC/C            | <b>precore/core protein</b>   | AXXATGc               | 0.56                     | 212             | 24.2                             | H <sub>2</sub> N- <b>M1'</b> -X28- <b>M1</b> -X64- <b>M2</b> -X26- <b>M3</b> -X90-COOH |
|                   | core isoform 1                | tXXATGa               | 0.11                     | 118             | 13.6                             | H <sub>2</sub> N- <b>M2</b> -X26- <b>M3</b> -X90-COOH                                  |
|                   | canonical core protein        | GXXATGG               | 0.09                     | 183             | 21                               | H <sub>2</sub> N- <b>M1</b> -X64- <b>M2</b> -X26- <b>M3</b> -X90-COOH                  |
|                   | core isoform 2                | AXXATGG               | 0.07                     | 91              | 10.6                             | H <sub>2</sub> N- <b>M3</b> -X90-COOH  |
| PreS1             | <b>canonical LS protein</b>   | AXXATGG               | 0.95                     | 400             | 43.7                             | H <sub>2</sub> N- <b>M1</b> -X118- <b>M2</b> -X54- <b>M3</b> -X225-COOH                |
|                   | MS protein isoform            | GXXATGc               | 0.24                     | 281             | 31                               | H <sub>2</sub> N- <b>M2</b> -X54- <b>M3</b> -X225-COOH                                 |
|                   | S protein isoform             | AXXATGG               | 0.18                     | 226             | 25.1                             | H <sub>2</sub> N- <b>M3</b> -X225-COOH   |
| S                 | <b>MS protein isoform</b>     | GXXATGc               | 0.54                     | 281             | 31                               | H <sub>2</sub> N- <b>M2</b> -X54- <b>M3</b> -X73- <b>M3'</b> -X151-COOH                |
|                   | S protein isoform             | AXXATGG               | 0.18                     | 226             | 25.1                             | H <sub>2</sub> N- <b>M3</b> -X73- <b>M3'</b> -X151-COOH                                |
|                   | S-smaller protein isoform     | tXXATGt               | 0.09                     | 152             | 17.2                             | H <sub>2</sub> N- <b>M3'</b> -X151-COOH  |
| XI                | <b>canonical HBx protein</b>  | cXXATGG               | 0.53                     | 154             | 16.5                             | H <sub>2</sub> N- <b>M1</b> -X77- <b>M2</b> -X25- <b>M3</b> -X49-COOH                  |
|                   | middle HBx isoform            | cXXATGG               | 0.08                     | 76              | 8.6                              | H <sub>2</sub> N- <b>M2</b> -X25- <b>M3</b> -X49-COOH                                  |
|                   | smaller/Mini HBx isoform      | tXXATGa               | 0.04                     | 50              | 5.8                              | H <sub>2</sub> N- <b>M3</b> -X49-COOH  |
| XII               | middle HBx Isoform            | cXXATGG               | 0.16                     | 76              | 8.6                              | H <sub>2</sub> N- <b>M2</b> -X25- <b>M3</b> -X49-COOH                                  |
|                   | smaller/Mini HBx isoform      | tXXATGa               | 0.04                     | 50              | 5.8                              | H <sub>2</sub> N- <b>M3</b> -X49-COOH  |

<sup>1</sup> <https://atgpr.dbcls.jp/>, [33].

<sup>2</sup> mRNA considering each individual viral canonical reading frame.

<sup>3</sup> In bold, each viral canonical reading frame.

<sup>4</sup> Reliability is the likelihood that the estimate will be achieved accurately.

<sup>5</sup> Canonical Met are in red, and potential Met isoforms are in bold.

**Table S2. Main characteristics of the Canonical and HBx isoform proteins.**

|                      | Name <sup>1</sup> | Amino acids <sup>2</sup> | Molecular weight, (kDa) <sup>2</sup> | Isoelectric point, (pI) <sup>2</sup> | Subcellular Location <sup>1</sup> |                   | Individual effect on HBV replication <sup>1,3</sup> |
|----------------------|-------------------|--------------------------|--------------------------------------|--------------------------------------|-----------------------------------|-------------------|---|
|                      |                   |                          |                                      |                                      | High abundance                    | Low abundance     |   |
| <b>Canonical HBx</b> | Wildtype          | 154                      | 16.6                                 | 8.91                                 | Cytoplasmic                       | Nuclear           | Activating  |
| <b>HBx XF</b>        | Full-length       | 154                      | 16.5                                 | 8.91                                 | Nucleocytoplasmic/<br>Nuclear     | Nucleocytoplasmic | Repressing  |
| <b>HBx XM</b>        | Middle            | 76                       | 8.6                                  | 8.82                                 | Nuclear                           | Cytoplasmic       | Repressing  |
| <b>HBx XS</b>        | Small, mini       | 50                       | 5.8                                  | 6.53                                 | Cytoplasmic                       | Cytoplasmic       | Activating  |

<sup>1</sup> As established in [142].

<sup>2</sup> Corresponding to HBx proteins from HBV subgenotype F1b, Genbank KM233681.1, 3215 bp [3, 4].

<sup>3</sup> As established in [159].