HBV Biology - a light(e)ning tour
HBV Genotype C Diversity - Pacific and Eurasia
Specific amino acid motifs found in a specific ethnic background.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Subtype/Genotype</th>
<th>Amino Acid Variant Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td><strong>SE-Asian</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>adr/C</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>adw2/B</td>
<td>S</td>
</tr>
<tr>
<td>Korea</td>
<td>adr/C</td>
<td>S</td>
</tr>
<tr>
<td>Japan</td>
<td>adr/C</td>
<td>S</td>
</tr>
<tr>
<td>Vietnam</td>
<td>ayw/1/B</td>
<td>S</td>
</tr>
<tr>
<td>Pacific</td>
<td>adrq-/C</td>
<td>S</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>adw2/A</td>
<td>T</td>
</tr>
<tr>
<td>Italy</td>
<td>adw2/A</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>ayw2/D</td>
<td>T</td>
</tr>
<tr>
<td>Scotland</td>
<td>adw2/A</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>ayw2/D</td>
<td>T</td>
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</tbody>
</table>
Nuclear Transport

cccDNA

HBV RNA transcripts

MINICHROMOSOME

Pol protein

Pregenomic RNA

pgRNA

Core proteins

Encapsulation of pgRNA and Pol

Envelope proteins S,M,L

ER

Golgi

Release

Receptor Mediated Endocytosis
Protein products of the surface gene

PreS$_1$  PreS$_2$  S

ATG   ATG   ATG   TAA

Small
middle
large

Viral attachment region
Hydrophilic region
Reactivation of hepatitis B during immunosuppressive lymphoma therapy

- Italian patient with B cell lymphoma since 1989, several therapies
- 1996 HBsAg neg., anti-HBc neg.
  - anti-HBs 612 IU/L; no vaccination
- In 2003 4 cycles of chemotherapy
- July 2003 under chemotherapy
  - HBsAg AxSym highly pos., not inhibitable
  - HBsAg VIDAS neg.
  - Anti-HBc neg., anti-HBs 93 IU/L
  - No hepatitis
  - HBV DNA $1.8 \times 10^8$ copies/mL
- Lamivudine therapy started
- Escape mutations: L109R, C137W, G145R

Communicated by R. Kaiser and H. Pfister, University Cologne
Genotype- and vaccine-escape induced specific exchanges in the α determinant of SHBs

Rituximab associated escape mutant

Conserved
Genotype-specific exchanges
Variable
Vaccine-induced exchanges
Subtype-specific alleles

Schaefer, 2001
Inhibition of HBsAg signals of a patient serum after neutralisation with anti-HBs sera from aHB-vaccinated donor (650 000 IU/L) or from a Sheep immunised with wt HBsAg genotypes A, D, C (40 000 IU)
Laurell Electrophoresis: detection of an HBsAg Escape* Variant Genotype D with a multivalent anti-HBs sheep antiserum raised with three genotypes

<table>
<thead>
<tr>
<th></th>
<th>Anti-wtA, D</th>
<th>Anti-wtA, D, C</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2x10^6 IU/L</td>
<td>4x10^4 IU/L</td>
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<table>
<thead>
<tr>
<th>HBsAg serum µg/ ml</th>
<th>A</th>
<th>Esc*</th>
<th>D</th>
<th>A</th>
<th>Esc</th>
<th>D</th>
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<tbody>
<tr>
<td></td>
<td>100</td>
<td>ca 50</td>
<td>20</td>
<td>100</td>
<td>1:3</td>
<td>20</td>
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</table>

*Escape mutations: L109R, C137W, G145R

Anti-HBs of the patient neutralised by HBsAg A or D, not C
HBV polymerase/RT

HBsAg

“a” determinant
Protein products of the core gene

Core promoter

ATG TAGATG

Pre-C C

ATG ATG TAG

Core protein

HBeAg
HBeAg and immunotolerance

HBeAg is:
- Not part of the virion
- A secreted protein
- Found in all hepadnaviruses
- Associated with high replication

In utero

infection

Tolerant child

birth
Pre-core mutants

• Usually found in DNA+ anti-HBe+ patients
• Selected after seroconversion to anti-HBe
• In certain genotypes only
• Do not always correlate with progression
• Associated with fulminant hepatitis (see below)
• Do not directly predict response to interferon
• No effect on nucleoside analogue therapy
HBeAg+ → HBeAg-WT core → mutant core

HBeAg- → B cell → Th cell

Cytopathic strains
mutations in other proteins
further core mutations
another immune response

Ongoing Disease

loss of immunomodulation
Does sequence dictate cellular localisation?

HBeAg Positive: No Mutation (Nuclear)

Anti-HBe Positive: B cell Epitope/C-terminus Mutations (Cytoplasmic)

Mutagenesis: B cell/C-terminus mutations Reversion to Wild type (Nuclear & Cytoplasmic)
Natural history of chronic HBV infection

Serology
- HBeAg
- Anti-HBe

DNA
- Pre-core variant

HBsAg
- Anti-HBc

HBV DNA

Limit of HBsAg detection

0 50 100 days 2 5 10 years
Distribution of HBV DNA load and relation to HBe Ag/Ab in HBsAg+ Ghanaian blood donors

Detection of HBV DNA in HBsAg positive samples

<table>
<thead>
<tr>
<th>Author</th>
<th>Sensitivity</th>
<th>DNA in HBsAg +</th>
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<tbody>
<tr>
<td></td>
<td>IU/ml</td>
<td>(%)</td>
</tr>
<tr>
<td>Jardi</td>
<td>1000</td>
<td>128/193 (66)</td>
</tr>
<tr>
<td>Loeb</td>
<td>10</td>
<td>164/195 (84)</td>
</tr>
<tr>
<td>Allain</td>
<td>20</td>
<td>156/159 (98)</td>
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</table>
Prevalence of anti-HBc only and HBV DNA frequency

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>No screened</th>
<th>Anti-HBc only (%)</th>
<th>DNA+ (%)</th>
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<tbody>
<tr>
<td>Hennig</td>
<td>Germany</td>
<td>14,251</td>
<td>20 (0.14)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Tseliou</td>
<td>Greece</td>
<td>10,629</td>
<td>507 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Zervou</td>
<td>Greece</td>
<td>6696</td>
<td>105 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Allain</td>
<td>UK</td>
<td>103,869</td>
<td>69 (0.07)</td>
<td>0</td>
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<tr>
<td>Kleinman</td>
<td>USA</td>
<td></td>
<td>387</td>
<td>4/107 (3.7)</td>
</tr>
<tr>
<td>Almeida-Neto</td>
<td>Brazil</td>
<td>112</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ren</td>
<td>China</td>
<td>297</td>
<td></td>
<td>1 (0.3)</td>
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<tr>
<td>Sato</td>
<td>Japan</td>
<td>540,161</td>
<td>1103 (0.2)</td>
<td>12 (1.1)</td>
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<tr>
<td>Bernvil</td>
<td>Saudi Arabia</td>
<td>6,035</td>
<td>125 (2.1)</td>
<td>4 (3.2)</td>
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<tr>
<td>Allain</td>
<td>Ghana</td>
<td>242</td>
<td>110 (45.5)</td>
<td>14 (12.7)</td>
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</table>
Hidden HBV infection in pre and post-vaccination sera in South Africa

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccination</th>
<th>Post-vaccination</th>
<th>p value</th>
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<tbody>
<tr>
<td>anti-HBs</td>
<td></td>
<td>893/986 (90.6%)*</td>
<td></td>
</tr>
<tr>
<td>anti-HBc</td>
<td>4/203 (1.9%)</td>
<td>9/986 (0.9%)</td>
<td>0.187</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>30/459 (6.5%)</td>
<td>4/1213 (0.3%)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

*Anti HBs reactivity is borderline in 59/986 (6%)*