Molecular epidemiology of HBV in SSA

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Phylogenetic analysis of human and ape HBV over time of evolution (Paraskevis D et al. Hepatol 2013)
Prevalence of HBsAg in the world
Prevalence of anti-HBc in the world

- **Canada**: < 1
- **United States**: < 1
- **Brazil**: 1 - 10
- **Russia**: < 1
- **Australia**: < 1
- **Indonesia**: 15 - 75
- **China**: 15 - 60
- **India**: 2 - 10
- **Philippines**: > 80
- **United States**: > 80
- **Canada**: < 1
- **Australia**: < 1
- **Indonesia**: 15 - 75
- **China**: 15 - 60
- **India**: 2 - 10
- **Philippines**: > 80
- **United States**: > 80
- **Canada**: < 1
- **Australia**: < 1
- **Indonesia**: 15 - 75
- **China**: 15 - 60
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- **Canada**: < 1
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- **Indonesia**: 15 - 75
- **China**: 15 - 60
- **India**: 2 - 10
- **Philippines**: > 80
- **United States**: > 80
- **Canada**: < 1
HBV inter-genotype recombinant forms
Distribution of HBsAg prevalence in first time blood donors in Africa

- <5%
- 5-10%
- >10%
Distribution of HBV genotypes in Africa

Number of samples
Tunisia = 79
Egypt = 105
Senegal = 32
The Gambia = 124
Côte d’Ivoire = 48
Ghana = 214
Benin = 20
Niger = 58
Nigeria = 163
Cameroon = 100
Kenya = 56; 18
Rwanda = 45
Malawi = 20
Angola = 40
Namibia = 23
South Africa = 23
Madagascar = 45
Potential historical evolution of HBV in the old world in the past 10,000 years
Distribution of HBV genotypes in Africans and African Americans

African American
- 85% A2
- 15% A1

Haïti
- A1 71%
- D 29%

Genotype distribution over time:
- 1833-45: A1
- Later: A2

Map showing the distribution of HBV genotypes around the world.
Possible evolution of HBV in the old world

Northern Africa and the Middle East

D subtype 1

D/E

E

A subtype 3

CRF A3/E

CRF E/D

300 years ago

A1

D subtype 7
Distribution of HBV genotypes in Ghana in 110 HBsAg + blood donors (Allain et al. Blood 2003)

- Genotype A: 7%
- Genotype D: 3%
- Genotype E: 90%
Phylogenetic analysis of full genome sequences from Guinea

- 81 full genome sequences
- Genotype A3 : 1 seq
- Genotype E : 76 seq
- Seq in blue: Recombinants
Evidence of recombination between HBV genotype E and A and E and D in strains originating from Guinea and Ghana

Red: genotype A
Blue: genotype E
Orange: genotype D
Schematic representation of Guinean and Ghanaian HBV A/E and E/D recombinant strains
Recombinant D/E in blood donors in Khartoum, Sudan

(a) S81

(b) Pre-S1

Recombination in blood donors in Khartoum, Sudan

(a) S81

(b) Pre-S1

Recombination in blood donors in Khartoum, Sudan
7 Guinean strains with core deletions
(Garmiri et al. J Gen Virol 2009; 90:2442-51)

A

\[ E\text{coRI} \]

Wild type

\[
\begin{array}{c}
\times 1 \\
1979 \quad 2241 \\
262 \text{ bp}
\end{array}
\]

\[
\begin{array}{c}
\times 2 \\
2007 \quad 2314 \\
49 \text{ bp} \quad 147 \text{ bp}
\end{array}
\]

\[
\begin{array}{c}
\times 4 \\
2010 \quad 2235 \\
37 \text{ bp} \quad 78 \text{ bp}
\end{array}
\]

1818 \quad 2454

B

Pre-core Core

Size (bp)

GU489 GU732 GU1086 GU1365 GU1405 GU1410 GU1520 + control - control HyperLadder I

Size (bp)

943 862 747 681
Viral Load distribution of HBsAg+ Guinean samples
Overview of the recombination and deletion points in West African strains

Deletions and recombinations occur in similar core regions suggesting preferential DNA re-arrangement in this area of HBV genome.
HBV splicing and mechanisms of replication and HBsAg production

Allain & Cox Curr Opin Hematol 2011; 18: 461-6

[Diagram showing the process of HBV splicing and replication, with key components and pathways labeled.]
Splicing sites and neo-proteins observed in HBV genotype D

# Total % splicing and % SP1 spliced DNA


<table>
<thead>
<tr>
<th>Genotype</th>
<th>Median viral load (IU/ml)</th>
<th>Mean % total spliced DNA</th>
<th>% Range</th>
<th>Mean % SP1 quantitative</th>
<th>Range % SP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 A</td>
<td>1.0x10^7</td>
<td>5.6</td>
<td>0-24</td>
<td>0.15</td>
<td>0.01-1.0</td>
</tr>
<tr>
<td>20 B</td>
<td>3.1x10^5</td>
<td>36.7</td>
<td>0-91</td>
<td>1.7</td>
<td>0.01-9.9</td>
</tr>
<tr>
<td>20 C</td>
<td>2.5x10^5</td>
<td>6.2</td>
<td>0-56</td>
<td>0.43</td>
<td>0.1-1.2</td>
</tr>
<tr>
<td>20 D</td>
<td>9.3x10^4</td>
<td>55.9</td>
<td>0-95</td>
<td>10.3</td>
<td>6.1-91.4</td>
</tr>
<tr>
<td>20 E</td>
<td>2.3x10^7</td>
<td>16.9</td>
<td>0-67</td>
<td>0.1</td>
<td>0.01-0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N samples</th>
<th>2</th>
<th>15</th>
<th>23</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>26</th>
<th>13</th>
</tr>
</thead>
</table>

![Graph showing viral load (copies/ml) vs. % of total samples tested](image-url)
Impact of spliced HBV DNA in viral load quantification and infectivity studies
## Modes of HBV transmission in various areas

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>NW Europe</th>
<th>Mediterranean</th>
<th>Asia</th>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertical</strong></td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Horizontal</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>- familial</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- hetero</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- homo</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- IVDU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- tattoo/scar.</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>- transfusion</td>
<td>±</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

### Prevalent genotype

- A/D
- D/A
- C/B
- E/D/A
Distribution of HBV DNA load and relation to HBe Ag/Ab in HBsAg+ Ghanaian blood donors

Prevalence of HBV infection in newborn, infants and young children

% of total

Age groups (months)

0-5m  6-11m  12-23m  24-35m  36-47m  47-70m
Distribution of HBV DNA load in adults (230) and children <6y (44)
Comparing genotype C and E
HBV markers in Ghanaian blood donors

- **HBsAg**
- **Anti-HBs**
- **Anti-HBc**

![Graph showing the percentage of total population with different HBV markers by age group.](image)

- **<20 years**:
  - HBsAg: ~15%
  - Anti-HBs: ~18%
  - Anti-HBc: ~84%

- **20-29 years**:
  - HBsAg: ~10%
  - Anti-HBs: ~20%
  - Anti-HBc: ~75%

- **30-39 years**:
  - HBsAg: ~5%
  - Anti-HBs: ~25%
  - Anti-HBc: ~70%

- **>40 years**:
  - HBsAg: ~3%
  - Anti-HBs: ~30%
  - Anti-HBc: ~67%
Natural history of HBV infection in Ghana

Vertical and horizontal infection

Sexual infection and re-exposure

Anti-HBc

Anti-HBs

HBsAg

Age (years)
Viral markers of HBV infection in 217 Ghanaian pregnant women

- HBsAg: 85% (occult HBsAg: 6%)
- HBV DNA: 9%

Total: 100%
Conclusions

• Genotype E infection generates frequent OBI of uncertain pathogenicity

• Pathogenicity of relatively frequent recombinant virus should be compared to genotype E

• 87.6% of infants being vaccinated, horizontal transmission should significantly decline (evidence?)

• Vertical transmission from few high VL mothers might remain a threat depending on vaccine schedule

• Most chronic infections having low VL, sexual transmission should remain low