

Occult Hepatitis B Virus Infection

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Disclosures

- No conflict-of-interest disclosures

Occult Hepatitis B Virus Infection: Introduction

- **Definition:** HBsAg-negative with detectable HBV DNA by PCR in serum or liver
 - **Seropositive:** Positive anti-HBc antibody +/- anti-HBs antibody
 - Vast majority of cases of occult hepatitis B
 - **Seronegative:** Undetectable anti-HBc and anti-HBs antibodies
- Unclear prevalence
 - Estimated prevalence anywhere from <1%-87% depending on study and population
 - Studies not comparable due to methodology differences

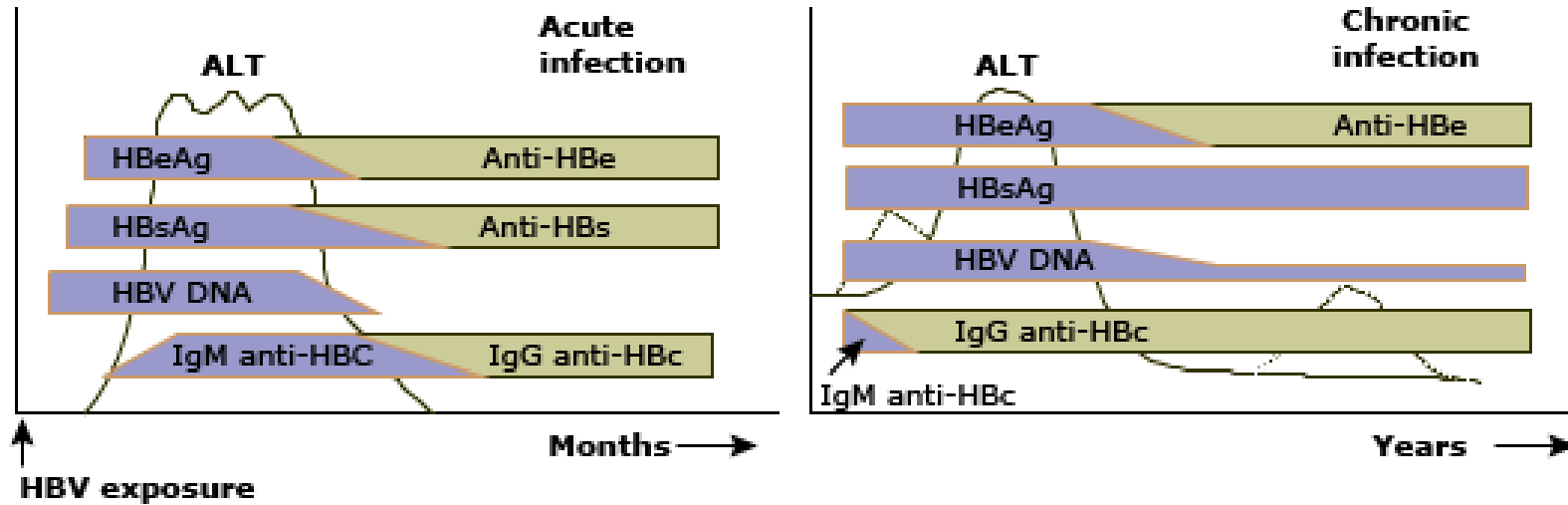
Occult Hepatitis B: Clinical Significance

- Associated with chronic liver disease
- May be associated with increased risk of hepatocellular carcinoma
 - Patients with chronic HCV infection
 - Patients from countries with high HBV prevalence
- Implications for blood transfusion and organ transplantation

Occult Hepatitis B: Clinical Settings

- Clinical settings where occult hepatitis B may be present:
 - During window period of acute HBV infection
 - In patient without known history of HBV infection
 - Consider in differential diagnosis for cryptogenic chronic liver disease, especially when HBV risk factors present
 - In patient with known history of HBV infection

Serologic responses to hepatitis B virus infection

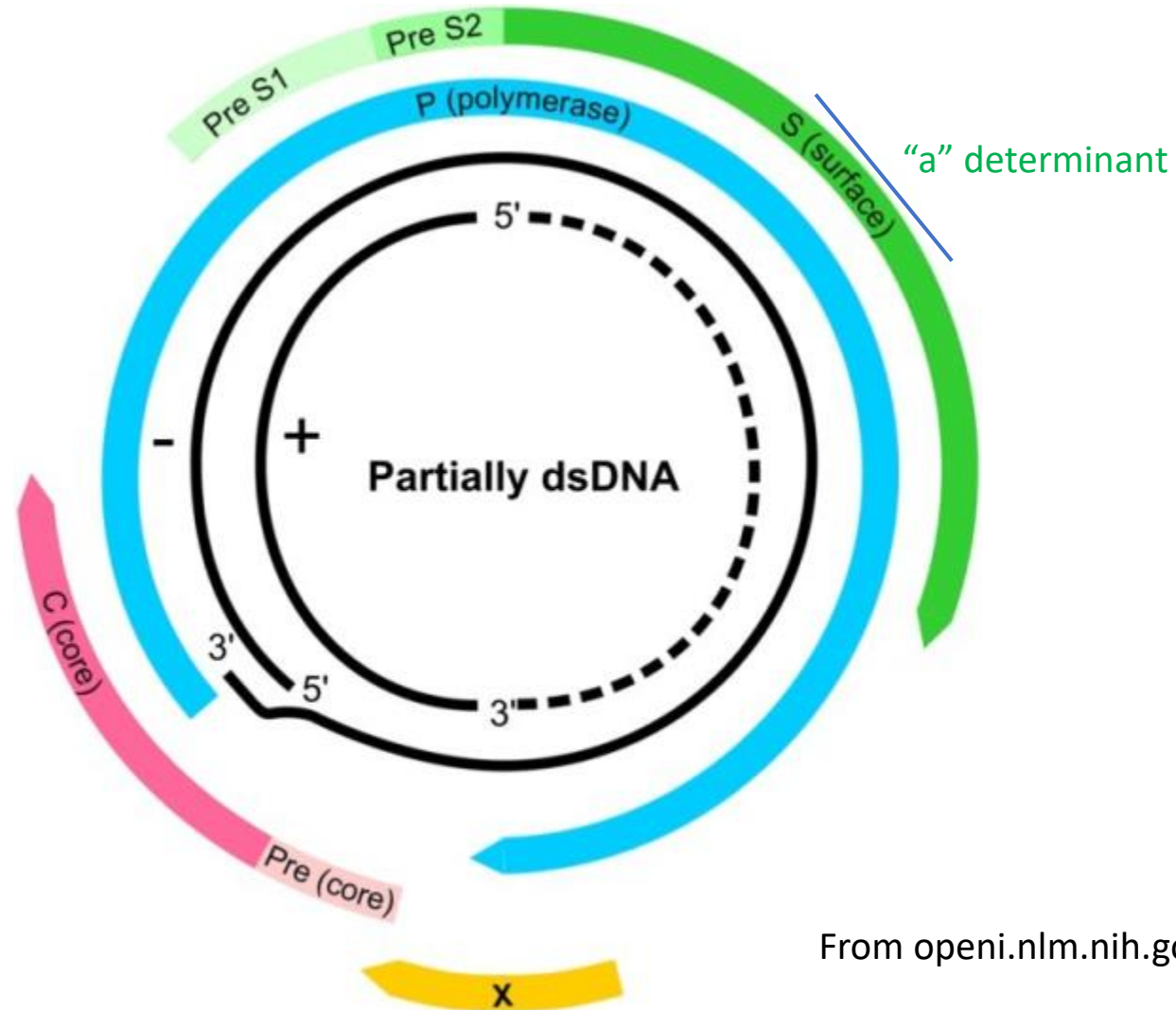


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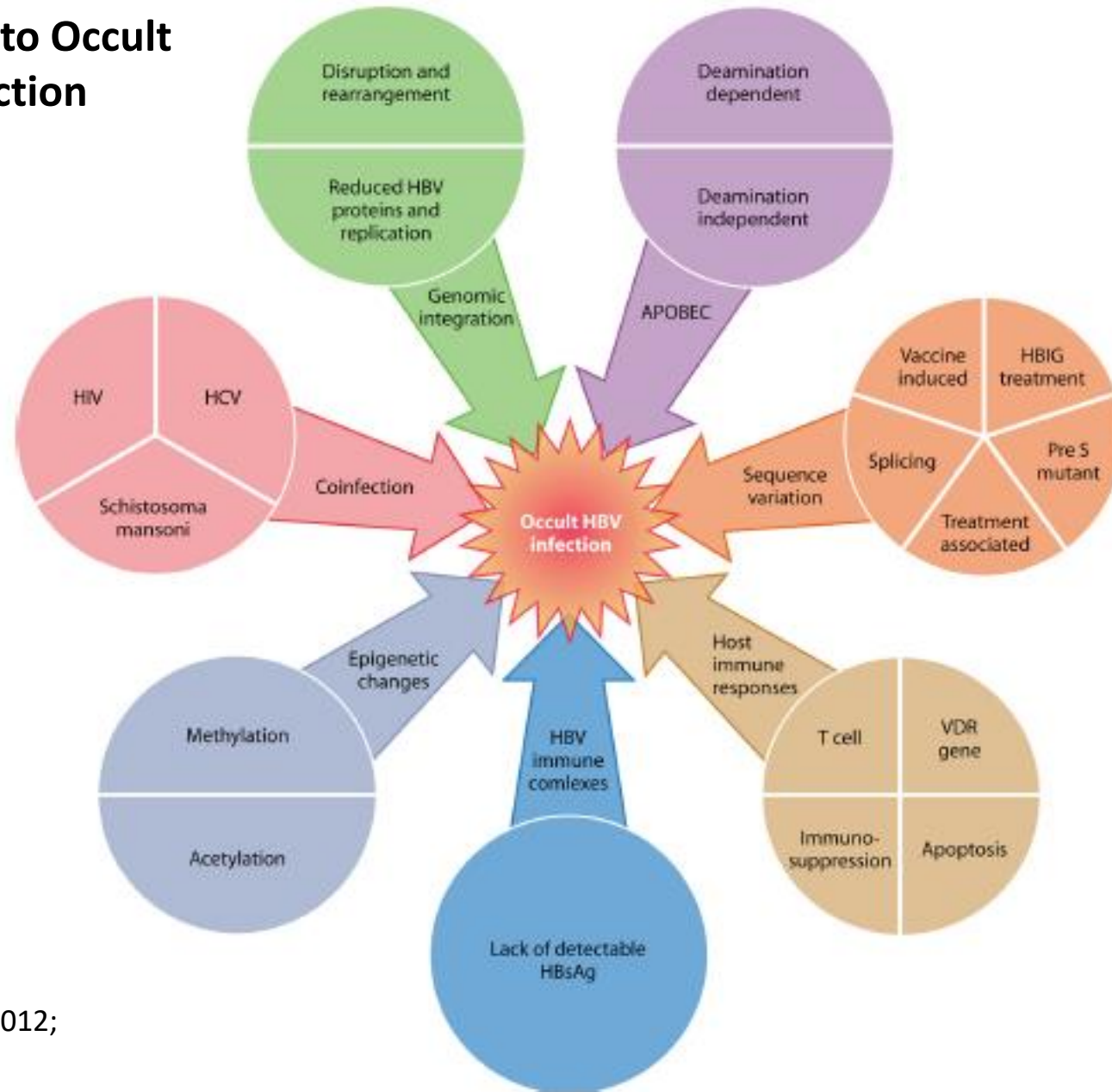
HBV Genome

- 3.2-kb Partially double stranded DNA virus
- 4 Overlapping open reading frames
- Hepadnavirus family



From openi.nlm.nih.gov

Mechanisms Leading to Occult Hepatitis B Virus Infection



From Samal J et al., *Clin Micro Rev* 2012;
25(1): 142-163

FIG 1 Overview of mechanisms leading to occult hepatitis B virus (HBV) infection.

Occult Hepatitis B: Causes

- **Very low level HBV viremia** resulting in detectable HBV DNA at low concentration with sub-detectable HBsAg
 - Most common cause
 - Multiple potential mechanisms
 - HBV mutations interfering with RNA splicing
 - G458A mutation in S gene leads to lack of HBsAg production and low viral replication
 - Pre-S gene mutations/deletions
 - Reduced HBV surface protein expression
 - Eliminate B-cell and T-cell epitopes leading to immune escape and viral persistence
- **HBV S (surface) gene mutations**
 - Rare cause
 - Vaccine escape mutants: mutations in “a” determinant of HBV S gene

HBV S gene Vaccine Escape Mutants

- Most common mutation
 - Glycine to arginine substitution at codon 145 (G145R) in “a” determinant of HBV S gene
- “a” determinant of HBV S gene
 - Major B-cell neutralizing epitopes of HBsAg
 - Antibodies to “a” determinant confer protection against all HBV serotypes
 - Mutations in “a” determinant may result in:
 - Immune/vaccine escape via decreased binding to HBsAb
 - Inability to detect HBsAg by lab assay

HBV S gene Vaccine Escape Mutants

- HBV S gene mutants found in infants infected with HBV despite adequate HBsAb response to vaccination
 - Data suggests S gene mutants selected by HBV vaccine and/or Hepatitis B immune globulin (HBIG)
 - Some evidence suggesting vertical transmission of S gene mutants from mother to baby

HBV Vaccine Escape Mutants: Experience in Taiwan

- 1984: Universal newborn HBV vaccination started in Taiwan
- Hsu HY et al., *Gut* 2004; 53(10): 1499-503
 - Prevalence of HBV S gene mutants in HBV DNA (+) children <15 yo in Taiwan
 - 1984: 7.8%
 - 1989: 19.6%
 - 1994: 28.1%
 - 1999: 23.1%
 - Absolute number children <15 yo with HBV S gene mutants
 - Stable through 1994
 - Decreased from 1994-1999
 - Overall chronic HBV prevalence in Taiwanese children <15 yo decreased from 9.8% in 1984 to 0.7% in 1999
 - Emergence of HBV S gene mutants did not decrease efficacy of HBV vaccine