Molecular genetic characterization of hepatitis epidemiology in Latvia

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Paul Pumpens

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Sequencing of viral genes and complete viral genomes

Results in:

• identification of viral genotype/subtype/mutants

• specification of diagnosis and prognosis

• elaboration of an optimal treatment strategy

and allow to follow the treatment efficacy
HBV genotypes predominant in Latvia
HBV genotypes predominant in Latvia

Sominskaya et al,
Open Hep. 2011
Mutants - result of external influences:
chemical reagents
radiation,
temperature
immune pressure

Variants - naturally occurring changes

“Quasispecies” - whole of mutants/variants
coexisting in a cell

Main classes of mutations

Immune escape mutants
Therapy escape mutants
Diagnosis escape mutants
Vaccine escape mutants
Hepatitis B virus
Mutants in Latvia

- preS1: Hepatocyte binding
- preS2: Hepatocyte binding?
- S: major B cell epitope “a”
- P: drug resistance

Identified in patients with acute fulminant chronic HBV infections. Special sort - mutants in immunosuppressed patients.
Basic core promoter mutation

Results in:
- increased host immune response
- diminished production of HBeAg
- increased viral replication and enhanced disease activity

is typical for:
- chronic hepatitis
- fulminant hepatitis
- immunosuppressed patients

Mutations: phase I

• diminished production of HBeAg
• increased host immune response
• increased viral replication and enhanced disease activity

is typical for:
- chronic hepatitis
- fulminant hepatitis
- immunosuppressed patients
Mutations: phase II
Elimination of HBe

preC mutations
1896 G - A (TAG)
1814, 1815 initiation codon
1874 nonsense
1862 missense frameshifts

pre-C stop mutation
• related to core gene mutations/deletions, which are associated with disease activity
• decreased interferon-alpha responsiveness
• associated with fulminant hepatitis (but not determining it!)

Chronic active Asymptomatic carriers
Core mutations correlate with the pre-core stop mutation active liver disease

mid-core deletions

- decrease recognition by CTLs
- contribute to immune escape
- diminish host response to alpha-interferon therapy
Mutations: immune escape are important for
• HBV prevention (vaccination)
• diagnosis

• 2% to 3% produce escape mutants increase the risk of perinatal HBV transmission are typical liver post-transplantation event (up to 50%)
• Full prevention of synthesis of the MHBs
• Point mutations, deletions, insertions
• Chronic hepatitis
• Fulminant hepatitis?
• HCC? (MHBs transactivation)

Del 17-22 aa
resistance to nucleoside analogues

- 1 of 10 patients exhibited YMDD variant at 24 weeks post-transplantation
- 14 to 32% of immuno-competent patients developed YMDD variant after 36 weeks of lamivudine treatment

Lamivudine resistance

YMDD - M552V
M552I
Domain B - L528M
### Patient N1

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#### 2007.10.31,
- **Lamivudine treatment**,  
- **viral load** 4.87 E2 IU/ml

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#### 2008.08.08,
- **Lamivudine treatment**,  
- **viral load** 1.36 E4 IU/ml

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#### 2008.12.29,
- **Lamivudine treatment**,  
- **viral load** 3.59 E7 IU/ml

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Mutations: gene X

1 154

HCC

- deletions 128-130
- 130-132
- mutations 130
- 131
- truncation

Silent (HBs neg)

- substitutions

Fulminant
Hepatitis B Virus Variants in Long-Term Immunosuppressed Renal Transplant Patients in Latvia

Intervirology 2005;48:192–200
DOI: 10.1159/000081748

Hepatitis B and C Virus Variants in Long-Term Immunosuppressed Renal Transplant Patients in Latvia

Irina Sominskaya\textsuperscript{a}, Marija Mihailova\textsuperscript{a}, Juris Jansons\textsuperscript{a}, Viktorija Emelyanova\textsuperscript{a}, Inese Folkmane\textsuperscript{b}, Eriks Smagris\textsuperscript{b}, Uga Dumpis\textsuperscript{b}, Rafails Rozentals\textsuperscript{b}, Paul Pumpens\textsuperscript{a}

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An unusually high number of HBV and HCV infections was recorded in a Latvian paediatric oncology ward during the time period 1996–2000.

Serum samples from 45 such patients and 3 from infected medical personnel were used for the study.

- The use of multidose vials of isotonic solution for washing intravenous catheters and preparation of intravenous injections was common at the time of infection of all patients.
- Changing of gloves after each patient was not strictly adhered to either.
An Outbreak of HBV and HCV Infection in a Paediatric Oncology Ward: Epidemiological Investigations and Prevention of Further Spread

Unrooted maximum likelihood (ML) phylogenetic tree of HBV core sequences

Unrooted maximum likelihood (ML) phylogenetic tree of HCV core sequences
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