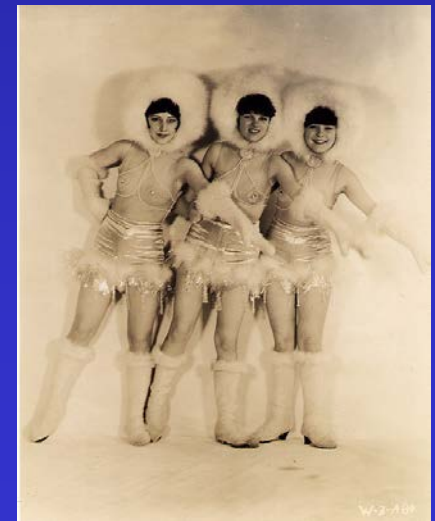


Classification of hepatitis B virus genotype B into 2 major types based on characterization of a novel subgenotype in Arctic indigenous populations



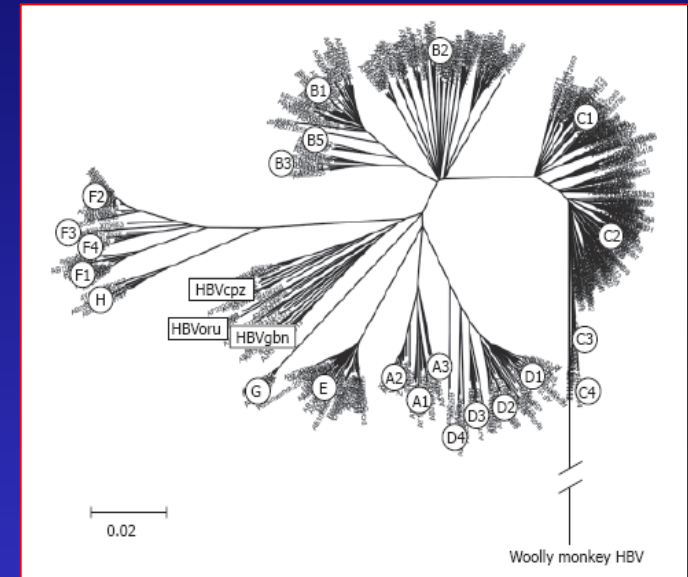
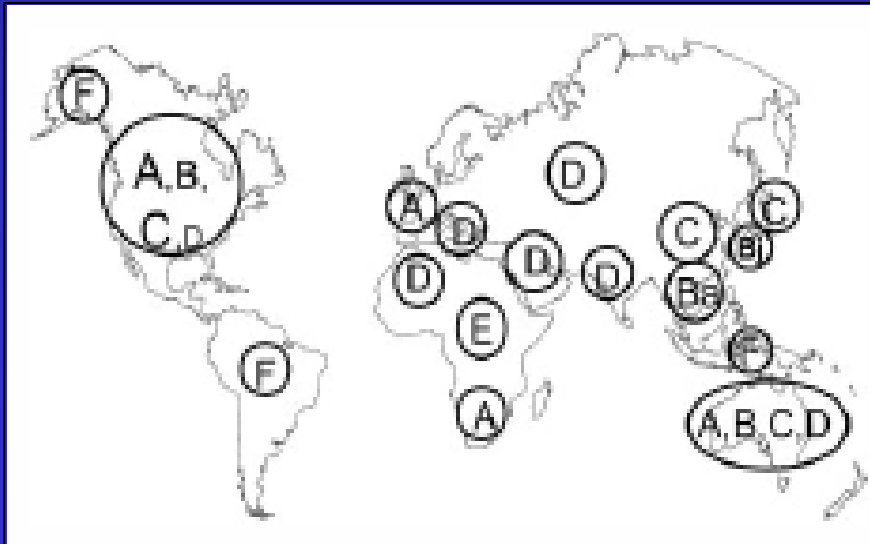
Viral Hepatitis Prevention Board Meeting, Copenhagen 2012

Anders Koch, Senior Researcher, PhD, MPH
Department of Epidemiology Research
Statens Serum Institut
Copenhagen, Denmark



Hepatitis B virus genotypes

- 8 major genotypes 'A' – 'H' and a number of subgenotypes
- Distinct geographic distribution
- F native American genotype



Genotype distribution in the Arctic (%)

	Alaska ¹ N=1157	Greenland ² N=93	Greenland ³ N=52
A	13	24	-
B	4	15	91
C	6	1	-
D	57	60	9
E	-	-	-
F	20	-	-

1. Livingstone et al. 2007
2. Børresen et al. 2011
3. Krarup et al. 2008



Rates of hepatocellular carcinoma (HCC) are different in Arctic populations

Area	ASR	SIR (95% CI) Connecticut	SIR (95% CI) Denmark	SIR (95% CI) Canada
Circumpolar	8.0	4.0 (3.0-5.2)	3.1 (2.2-4.3)	4.1 (3.0-5.3)
Alaska	15.1	7.2 (5.1-9.9)	5.5 (3.9-7.6)	7.7 (5.2-10.2)
Greenland	5.7	2.7 (1.5-4.5)	2.1 (1.2-3.4)	2.8 (1.5-4.5)
Canada	1.0	0.4 (0.0-2.2)	0.3 0.0-1.7	0.4 0.0-2.1

HBV genotypes and disease association in Alaska

- A HCC and active liver disease in older individuals
- B -
- C Cirrosis and HCC
- D HCC and active liver disease in older individuals, HBV vasculitis
- F HCC in young persons
- H -

Questions raised

- HBV genotype distribution different in Alaska and Greenland
 - F frequent in Alaska, not in Greenland
 - B frequent in Greenland, not in Alaska
- Incidence of HCC high in Alaska, low in Greenland
- HBV genotypes related to morbidity in Alaska
 - F related to HCC in young persons
- What is the impact on genotype B on liver disease in the Arctic?

Two major subtypes of Hepatitis B virus genotype B

Bj ('Japan')	B1	Non-recombinant	Less commonly associated with HCC
Ba ('Asia')	B2	Intergenomic recombination with HBV/C in core promoter/precore/-core genome region	Higher risk of HCC development in HBV carriers
	B3		
	B4		
	B5		

Sugachi et al. J Virol 2002
Sakamoto et al. J Gen Virol 2006
Sugauchi et al. Gastroenterology 2003
Kao et al. Gastroenterology 2000
Orito et al. Hepatology 2001

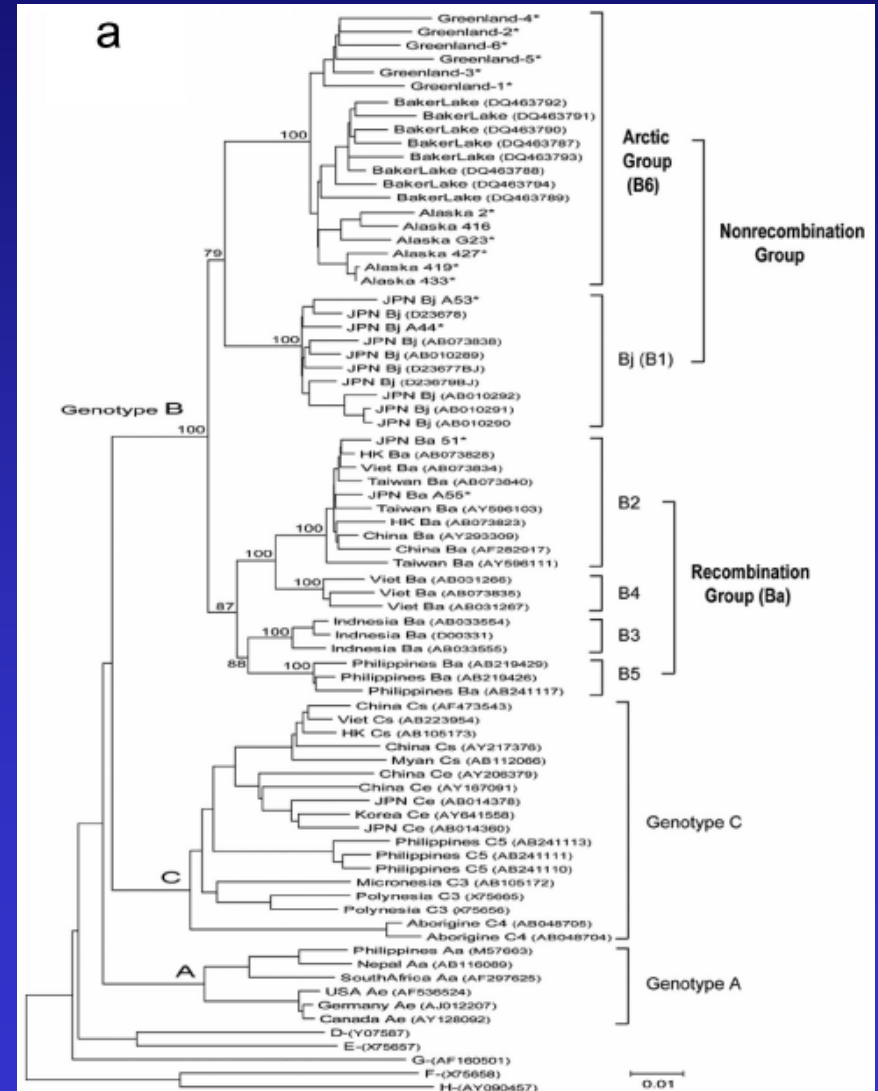
Comparative study of HBV B subgenotypes in the Arctic 2007

- 50 HBV carriers
 - Alaska: 31
 - Canada (Baker lake): 8
 - Greenland (Sisimiut): 11
- All native persons
- No HCV or HIV co-infection
- Classification
 - Asymptomatic
 - Chronic liver disease
 - Cirrhosis or HCC

- 20/50 HBV strains complete genome sequenced
 - 6 Alaska
 - 8 Canada
 - 6 Greenland
- All 50 HBV strains amplified in EnhII/Cp/preC/C regions
- Comparisons with bank HBV sequences from Asia

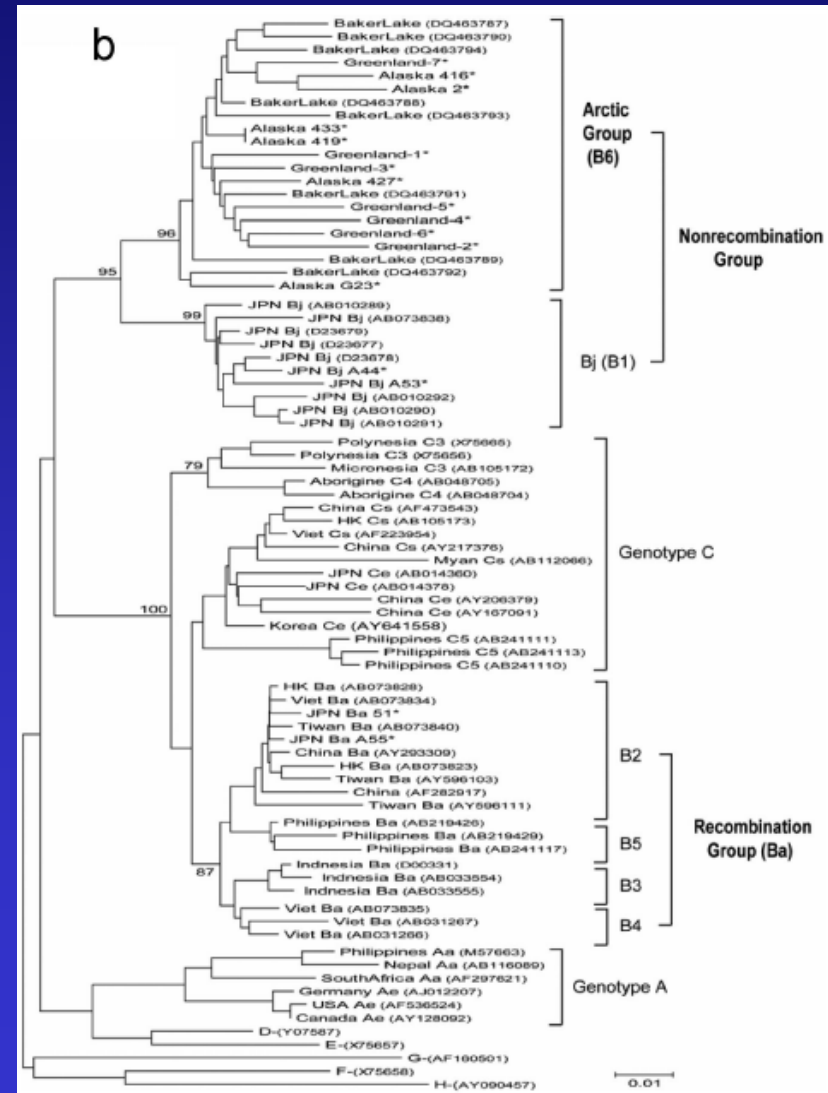
Phylogenesis based on complete genome sequences

- Asian/Japanese/Arctic HBV strains in 6 distinct clusters
- Asian/Japanese strains in known clusters Bj/B₁ + Ba/B₂-B₅
- All Arctic strains in distinct separate (unclassified) cluster
- Suggested designation B6



Phylogenesis based only on Cp/preC/C genomic regions

- Arctic strains very similar to Japanese B_j/B₁ strains
- Major split between non-recombinant and recombinant types
- Authors' suggestions:
 - New subgenotype 'B6'
 - Classification of HBV/B genotype into 2 major types, 'Non-Recombinant' B₁ + B₆, and 'Recombinant' B₂-B₅



Morbidity and HBV/B subgenotypes

Feature	HBV/B6 (n = 50)	HBV/Bj (n = 50)	HBV/Ba (n = 50)	P
Male sex	33 (66)	34 (68)	36 (72)	Matched
Age, mean ± SD, years	48.1 ± 19.6	48.1 ± 16.9	47.9 ± 13.1	Matched
Hepatitis B e antigen *	6 (12)	8 (16)	20 (40) ^a	<.02
DNA >5 log copies/mL *	9 (18%)	18 (36)	36 (72) ^b	<.001
Alanine transaminase *	40.3 ± 36.3	43.1 ± 33.4	94.0 ± 94.1 ^c	<.001
Clinical state				
Asymptomatic	35 (61) ^d	22 (44)	15 (30)	<.02
Chronic hepatitis *	15 (30)	24 (50)	21 (42)	NS
Liver cirrhosis/hepatocellular carcinoma *	0	4 (8)	14 (28) ^e	<.03

NOTE. Data are no. (%) of participants, unless otherwise indicated. HBeAg, hepatitis B e antigen; NS, no significant difference.

^a For B6 vs. Ba, $P = .0026$; for Bj vs. Ba, $P = .0143$.

^b For B6 vs. Ba, $P < .0001$; for Bj vs. Ba, $P = .0006$.

^c For B6 vs. Ba, $P = .0006$; for Bj vs. Ba, $P = .0005$.

^d For B6 vs. Ba, $P = .0001$; for B6 vs. Bj, $P = .0154$.

^e For B6 vs. Ba, $P < .0001$; for Bj vs. Ba, $P = .0214$.

Hypothesis: Co-existence of HBV B genotype and Eskimos

- Eskimos migrated from East Asia/Siberia to Alaska 10,000 BC
- Later developed into 3 groups
 - Aleutians (Aleuts, West Alaska)
 - Yupik (West Alaska)
 - Inuit (North Alaska, Canada & Greenland)
- The Inuit spread eastwards from Alaska 1,000 AD
- Subgenotype B6 followed the Eskimos from Asia?
 - Developed from B1?
 - Common forefather of B1/B6?



— HBV genotypes B1/B6
— HBV genotype F

Conclusions

- A new HBV/B subgenotype B6 identified
- All 50 Arctic HBV/B strains belonging to that subgenotype
- Related to the non-recombinant Japanese Bj/B1 subgenotype and different from recombinant Asian Ba/B2-B5 subgenotypes
- Non-recombinant B1 & B6 appear less virulent than B2-B5
- Classification of HBV/B into recombinant and non-recombinant forms
- B6 May have followed the Eskimos from Asia
- Larger studies on clinical manifestations of B6 needed

