

Description of a New Hepatitis B Virus C6 Subgenotype Found in the Papua Province of Indonesia and Suggested Renaming of a Tentative C6 Subgenotype Found in the Philippines as Subgenotype C7

Hepatitis B virus (HBV) genotypes (2, 4, 5, 7–9) and subgenotypes (11, 13, 14, 16–18) are important factors that influence the course of the disease and the outcome of treatment. Because of the clinical importance of the HBV classification, an accurate assignment of newly found subgenotypes to their respective clades and an unambiguous nomenclature are needed. A new HBV subgenotype should differ from previously established by at least 4%, and the segregation into a new clade should be supported by robust bootstrapping data (3).

In the June 2009 issue of the *Journal of Clinical Microbiology*, a new C6 subgenotype of HBV found in the Papua province of Indonesia (C6 Papua-Indonesia) is described (15). However, a tentative C6 subgenotype found in the Philippines (C6 Philippines) has already been published contemporaneously (1). To keep up with an unambiguous system of HBV subgenotypes, it is important to analyze if C6 Papua-Indonesia and C6 Philippines are identical or map to different clades.

Using methods described by Cavinta et al. (1) and published sequences from Utsumi et al. (15), we made a phylogenetic analysis using whole genomes that clearly showed that both C6 groups mapped to different clades (Fig. 1).

C6 Papua-Indonesia and C6 Philippines differed by 5.1% from each other and diverged by at least 4.1% from the other HBV subgenotypes (Table 1).

Thus, both contemporaneously described subgenotypes (1, 15) fulfill all criteria for having new and separate subgenotypes. Because the designation C6 has been claimed for partial sequences found in the Papua province of Indonesia already (6), we suggest that the subgenotype C6 found in the Papua province of Indonesia shall keep the designation C6, whereas the tentative subgenotype from the Philippines shall be called C7. To avoid similar confusion in the future, we have suggested a procedure that would involve the International Committee for Taxonomy of Viruses to allot new genotype/subgenotype designations (10).

REFERENCES

- Cavinta, L., J. Sun, A. May, J. Yin, M. von Meltzer, M. Radtke, N. G. Barzaga, G. Cao, and S. Schaefer. 2009. A new isolate of hepatitis B virus from the Philippines possibly representing a new subgenotype C6. *J. Med. Virol.* **81**:983–987.
- Chu, C. J., and A. S. Lok. 2002. Clinical significance of hepatitis B virus genotypes. *Hepatology* **35**:1274–1276.
- Kramvis, A., K. Arakawa, M. C. Yu, R. Nogueira, D. O. Stram, and M. C. Kew. 2008. Relationship of serological subtype, basic core promoter and precore mutations to genotypes/subgenotypes of hepatitis B virus. *J. Med. Virol.* **80**:27–46.
- Kramvis, A., M. Kew, and G. Francois. 2005. Hepatitis B virus genotypes. *Vaccine* **23**:2409–2423.
- Kramvis, A., and M. C. Kew. 2005. Relationship of genotypes of hepatitis B virus to mutations, disease progression and response to antiviral therapy. *J. Viral Hepat.* **12**:456–464.
- Lusida, M. I., V. E. Nugrahaputra, Soetjipto, R. Handajani, M. Nagano-Fujii, M. Sasayama, T. Utsumi, and H. Hotta. 2008. Novel subgenotypes of hepatitis B virus genotypes C and D in Papua, Indonesia. *J. Clin. Microbiol.* **46**:2160–2166.
- Miyakawa, Y., and M. Mizokami. 2003. Classifying hepatitis B virus genotypes. *Intervirology* **46**:329–338.
- Norder, H., A.-M. Couroucé, P. Coursaget, J. M. Echevarria, S.-D. Leef, I. K. Mushahwar, B. H. Robertson, S. Locarnini, and L. O. Magnius. 2004. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. *Intervirology* **47**:289–309.
- Schaefer, S. 2005. Hepatitis B virus: significance of genotypes. *J. Viral Hepat.* **12**:111–124.
- Schaefer, S. Under construction. Classification of hepatitis B virus genotypes and subgenotypes. *Intervirology*, in press.
- Sung, J. J. Y., S. K. W. Tsui, C.-H. Tse, E. Y. T. Ng, K.-S. Leung, K.-H. Lee, T. S. K. Mok, A. Bartholomeusz, T. C. C. Au, K. K. F. Tsoi, S. Locarnini, and H. L. Y. Chan. 2008. Genotype-specific genomic markers associated with primary hepatomas, based on complete genomic sequencing of hepatitis B virus. *J. Virol.* **82**:3604–3611.
- Tamura, K., J. Dudley, M. Nei, and S. Kumar. 2007. MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. *Mol. Biol. Evol.* **24**:1596–1599.
- Tanaka, Y., M. Mukaide, E. Orito, M. F. Yuen, K. Ito, F. Kurbanov, F. Suguchi, Y. Asahina, N. Izumi, M. Kato, C. L. Lai, R. Ueda, and M. Mizokami. 2006. Specific mutations in enhancer II/core promoter of hepatitis B virus subgenotypes C1/C2 increase the risk of hepatocellular carcinoma. *J. Hepatol.* **45**:646–653.
- Truong, B. X., Y. Yano, Y. Seo, T. M. Phuong, Y. Tanaka, H. Kato, A. Miki, T. Utsumi, T. Azuma, N. K. Trach, M. Mizokami, Y. Hayashi, and M. Kasuga. 2007. Variations in the core promoter/pre-core region in HBV genotype C in Japanese and Northern Vietnamese patients. *J. Med. Virol.* **79**:1293–1304.
- Utsumi, T., M. I. Lusida, Y. Yano, V. E. Nugrahaputra, M. Amin, Juniastuti, Soetjipto, Y. Hayashi, and H. Hotta. 2009. Complete genome sequence and phylogenetic relatedness of hepatitis B virus isolates in Papua, Indonesia. *J. Clin. Microbiol.* **47**:1842–1847.
- Wang, Z., J. Hou, G. Zeng, S. Wen, Y. Tanaka, J. Cheng, F. Kurbanov, L. Wang, J. Jiang, N. V. Naoumov, M. Mizokami, and Y. Qi. 2007. Distribution and characteristics of hepatitis B virus genotype C subgenotypes in China. *J. Viral Hepat.* **14**:426–434.
- Wang, Z., Y. Tanaka, Y. Huang, F. Kurbanov, J. Chen, G. Zeng, B. Zhou, M. Mizokami, and J. Hou. 2007. Clinical and virological characteristics of hepatitis B virus subgenotypes Ba, C1, and C2 in China. *J. Clin. Microbiol.* **45**:1491–1496.
- Yuan, J., B. Zhou, Y. Tanaka, F. Kurbanov, E. Orito, Z. Gong, L. Xu, J. Lu, X. Jiang, W. Lai, and M. Mizokami. 2007. Hepatitis B virus (HBV) genotypes/subgenotypes in China: mutations in core promoter and precore/core and their clinical implications. *J. Clin. Virol.* **39**:87–93.

Lolita Cavinta

*Department of Medical Microbiology
 College of Public Health
 University of the Philippines Manila
 Pedro Gil St.
 Manila, Philippines*

Guangwen Cao

*Department of Epidemiology
 Second Military Medical University
 800 Xiangyin Rd.
 Shanghai 200433, People's Republic of China*

Stephan Schaefer*

*Universität Rostock
 Medizinische Fakultät
 Institut für Medizinische Mikrobiologie, Virologie und Hygiene
 Abteilung für Virologie
 Schillingallee 70
 D-18057 Rostock, Germany*

*Phone: 0381-494-5920

Fax: 0381-494-5925

E-mail: stephan.schaefer@med.uni-rostock.de

Ed. Note: The authors of the published article declined to submit a response.

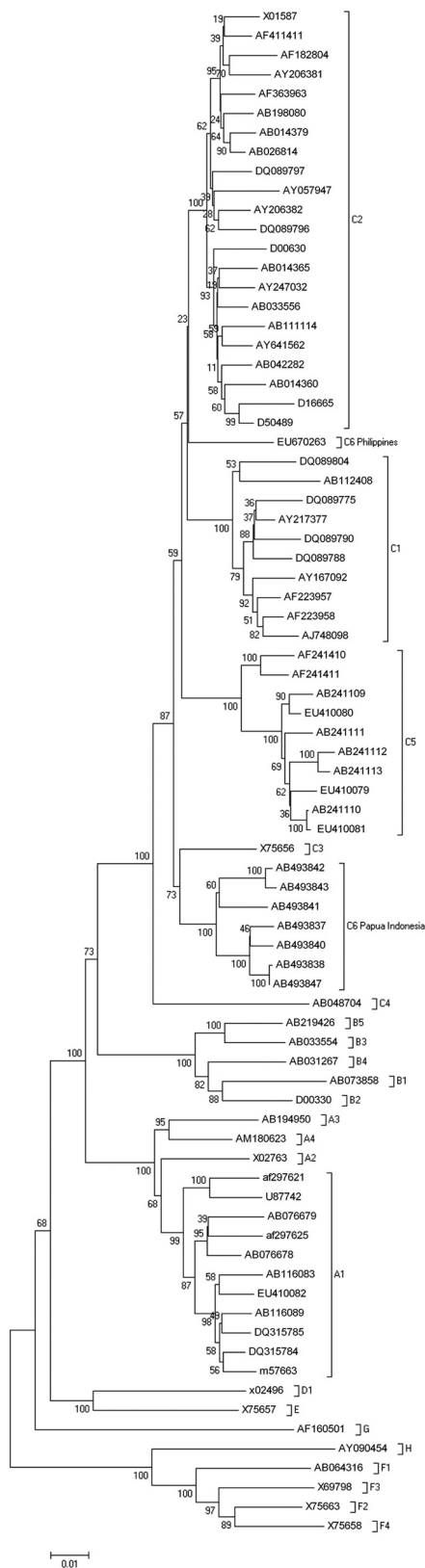


FIG. 1. Phylogenetic tree of complete HBV genomes of genotypes A to H. An alignment of complete sequences was performed with ClustalW using the program DNASTAR. The alignment was further analyzed by bootstrapping with 500 replicates, using the neighborhood-joining method contained in MEGA version 4.0 (12).

^a The comparisons were performed over the complete genome with the Kimura two-parameter model using MEGA version 4.0 (12). Between groups, the average was calculated.

Genotype/ subgenotype strain	Nucleotide distance between strains ^a																								
	A1	A2	A3	A4	B1	B2	B4	B5	C2	C3	C4	C5	C6 Papua- Indonesia	C6 Philippines	D1	E	F1	F2	F3	F4	G	H	C1	B3	
A1																									
A2	0.049																								
A3	0.051	0.054																							
A4	0.046	0.046	0.040																						
B1	0.100	0.096	0.102	0.098																					
B2	0.098	0.096	0.099	0.095	0.046																				
B4	0.100	0.097	0.100	0.097	0.055	0.039																			
B5	0.102	0.098	0.103	0.097	0.065	0.048	0.093																		
C2	0.092	0.089	0.092	0.084	0.105	0.095	0.093	0.091																	
C3	0.095	0.091	0.093	0.086	0.104	0.094	0.091	0.093	0.044																
C4	0.106	0.102	0.103	0.095	0.118	0.107	0.105	0.107	0.069	0.065															
C5	0.092	0.092	0.096	0.089	0.112	0.100	0.097	0.098	0.055	0.060	0.084														
C6 Papua-Indonesia	0.098	0.097	0.098	0.091	0.111	0.101	0.100	0.099	0.048	0.045	0.071	0.066													
C6 Philippines	0.092	0.091	0.093	0.084	0.106	0.094	0.090	0.090	0.041	0.047	0.072	0.059	0.051												
D1	0.106	0.103	0.102	0.102	0.119	0.112	0.111	0.112	0.107	0.106	0.113	0.108	0.118	0.103											
E	0.101	0.100	0.102	0.095	0.118	0.112	0.111	0.113	0.106	0.097	0.113	0.107	0.111	0.104	0.078										
F1	0.148	0.149	0.154	0.144	0.156	0.151	0.151	0.155	0.146	0.147	0.151	0.149	0.147	0.149	0.153	0.140									
F2	0.148	0.145	0.153	0.150	0.155	0.150	0.147	0.150	0.145	0.142	0.153	0.143	0.144	0.142	0.149	0.142	0.060								
F3	0.157	0.159	0.158	0.154	0.158	0.152	0.152	0.155	0.146	0.142	0.151	0.148	0.145	0.143	0.150	0.141	0.059	0.049							
F4	0.152	0.151	0.155	0.154	0.158	0.150	0.150	0.150	0.153	0.145	0.157	0.149	0.152	0.151	0.145	0.143	0.067	0.041	0.051						
G	0.118	0.118	0.121	0.115	0.138	0.133	0.128	0.129	0.129	0.131	0.146	0.129	0.134	0.132	0.120	0.115	0.158	0.155	0.154	0.051					
H	0.156	0.154	0.161	0.156	0.162	0.155	0.158	0.158	0.152	0.154	0.157	0.160	0.153	0.150	0.149	0.153	0.089	0.090	0.091	0.098	0.157				
C1	0.095	0.095	0.095	0.088	0.110	0.098	0.095	0.094	0.047	0.055	0.079	0.063	0.061	0.150	0.110	0.110	0.150	0.145	0.149	0.153	0.158	0.130			
B3	0.103	0.096	0.104	0.100	0.066	0.047	0.043	0.031	0.092	0.091	0.109	0.100	0.100	0.092	0.108	0.114	0.157	0.152	0.155	0.148	0.154	0.159	0.093		