World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i24.7665

World J Gastroenterol 2014 June 28; 20(24): 7665-7674
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (9): Hepatitis B virus

Hepatitis B virus lineages in mammalian hosts: Potential for bidirectional cross-species transmission

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Supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico of Brazil, No. 303422/2010-6
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Received: November 1, 2013 Revised: January 30, 2014
Accepted: March 12, 2014
Published online: June 28, 2014

Abstract

The hepatitis B virus (HBV) is a cosmopolitan infectious agent currently affecting over 350 million people worldwide, presently accounting for more than two billion infections. In addition to man, other hepatitis virus strains infect species of several mammalian families of the Primates, Rodentia and Chiroptera orders, in addition to birds. The mounting evidence of HBV infection in African, Asian and neotropical primates draws attention to the potential cross-species, zoonotic transmission of these viruses to man. Moreover, recent evidence also suggests the humans may also function as a source of viral infection to other mammals, particularly to domestic animals like poultry and swine. In this review, we list all evidence of HBV and HBV-like infection of nonhuman mammals and discuss their potential roles as donors or recipients of these viruses to humans and to other closely-related species.

Key words: Hepatitis B; Hepatitis B virus nonhuman host; Cross-species transmission; Hepatitis B virus

Core tip: Hepatitis B virus (HBV) is an infectious agent affecting humans worldwide. Other HBV-related strains infect mammalian species of primates, rodents and bats, in addition to birds. Evidence of HBV infection in African, Asian and Neotropical primates draws attention to potential cross-species transmission of these viruses to man. Mounting evidence suggests humans may also be a source of viral infection to other mammals, particularly to domestic animals like poultry and swine. We list evidence of HBV and HBV-like infection of nonhuman mammals and discuss their potential roles as donors/recipients of these viruses to humans and to other closely-related species.

Bonvicino CR, Moreira MA, Soares MA. Hepatitis B virus lineages in mammalian hosts: Potential for bidirectional cross-species transmission. *World J Gastroenterol* 2014; 20(24): 7665-7674 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i24/7665.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i24.7665

GENETIC DIVERSITY AND GEOGRAPHICAL DISTRIBUTION OF HEPATITS B VIRUSES

Hepatitis B is a serious public health problem worldwide because over two billion people have been already infected and more than 350 million are currently chronic carriers of the hepatitis B virus (HBV), accounting for one to two million deaths per year[1-4]. It is estimated that over half of hepatocellular carcinomas (HCC) worldwide are caused by HBV infection[5], a condition with an unfavorable prognosis representing the sixth most common malignancy worldwide and the third most frequent cause of death due to cancer[2]. Among chronic hepatitis B car-

riers, approximately 75% live in Asia[4] and 11 million in Latin America[6]. About one third of chronic hepatitis B carriers develop cirrhosis and HCC[7].

HBV prevalence varies worldwide, with countries showing high (> 8%), intermediate (2%-8%) and low (< 2%) estimates. In areas of high prevalence, approximately 70%-90% of the population has been infected by HBV before the age of 40 and 8% are chronic carriers[8,9]. Approximately 45% of the world population live in areas of high endemicity[2,8], including southeast Asia, the Pacific (excluding Japan, Australia and New Zealand), sub-Saharan Africa, Amazonia, Middle East regions, Central Asian republics, the Arctic and some east European countries. Low prevalence regions include North America, western and northeastern Europe, Australia and some parts of South America while the remaining world regions show an intermediate prevalence[2,9]. Among indigenous populations of the United States, Canada, New Zealand and Australia, HBV prevalence has been found to be above 5%[3].

HBV classification followed a historical chronology since its initial identification in humans. The first criterion of classification was based on the viral surface antigen, hepatitis B surface antigen (HBsAg). The determinant "a" (HBsAg amino acid residues 124 to 147) is common to all human HBV isolates and does not provide discriminating information. On the other hand, residues 122 and 160 are used to classify the second and the third determinants, and their combination is used for determining HBV subtypes. The four major subtypes are further subdivided, adding up to a total of ten described subtypes: ayw1, ayw2, ayw3, ayw4, ayr, adw2, adw3, adw4q-, adrq+ and adrq-[10].

Currently, HBV classification is based on viral genotypes and clades derived from phylogenetic analyses of partial or full-length nucleotide sequences. When whole genomes are compared, the established nucleotide divergence must be of at least 7.5% for defining a genotype while a classification exclusively based on the S gene requires at least a 4% divergence[11]. To present, eight different HBV genotypes have been described based on full-length sequences, named A to H[1]. Genotype I has been proposed for HBV samples found in Laos and Vietnam[12] but its formal recognition is still controversial. Another new genotype, named J, has also been recently described in a Japanese individual[13] but it has not been consensually accepted.

Genotypes diverging between 4% and 7.5% are further subdivided in to sub-genotypes A1 to A5, B1 to B8, C1 to C7, D1 to D7 and F1 to F4. A sub-genotype D8 has been recently proposed, resulting from a recombination event between HBV/D and HBV/E genotype, and circulating in Niger[1]. Two F sub-genotypes are further divided in two clades, F1 (a-d) and F2 (a and b)[11].

HBV genotypes predominate in different geographic regions. HBV/A and HBV/D are worldwide distributed while HBV/B and HBV/C are prevalent in Asia, Oceania and North America, HBV/E in Africa, HBV/F in Latin America, HBV/G in Central America and Europe, and HBV/H in Central America[11]. Genotypes A, D and F are the most prevalent among HBV carriers in South America[14,15], and only in Latin America the conjoint circulation of these three genotypes occurs in a large scale[14].

Many HBV genotypes co-circulate in different regions where an increased risk of co-infections has been observed, particularly with HBV/B and C and with HBV/A and D. As viral recombination necessarily presumes co-infection with at least two different genotypes, areas of co-circulation show increased rates of HBV genomic recombination[1,13]. Recombination often occurs in the pre-C/C genomic region and several recombinants have been described between HBV genotypes A and D, B and C, and A and C. In the case of B/C recombinants, two divergent viral strains with different geographic distribution have been identified and assigned to different B sub-genotypes[16].

HBV infection in nonhuman hosts

HBV belongs to the Hepadnaviridae family comprising two genera: Orthohepadnavirus and Avihepadnavirus, the former infecting mammals and the latter infecting birds. Orthohepadnaviruses have been identified in several mammals, including the woodchuck (*Marmota monax*), the ground squirrel (*Spermophilus beecheyi*), the artic ground squirrel (*Spermophilus parryii*), the pig (*Sus scrofa*), the neotropical wooly monkey (*Lagothrix lagothricha*), and Old World primate genera like *Gorilla*, *Pongo*, *Hylobates*, *Nomascus* and *Pan* (Table 1, Figure 1). Like most hepadnaviruses, HBV only replicates in specific hosts, although cross-species transmission between hosts of different species has been constantly occurred, representing a matter of concern in view of the ability of HBV to cross species barriers despite its genetic divergence[17,18]. Evidence of recombination between human and ape HBV and different nonhuman primate variants suggested that these viruses are capable of sharing hosts in natura[19-21].

A short genome length with overlapping coding regions and genome replication with an intermediate RNA molecule that is retrotranscribed by a viral reverse transcriptase are singular characteristics of hepadnaviruses. It might be initially assumed that these characteristics might restrict HBV of evolving too drastically despite its large host diversity. A combination of two, non-exclusive models can be proposed for HBV evolution: host-viral co-evolution and cross-species transmission. The divergence observed in avian and mammalian hepadnaviruses and the exclusive characteristics of each group, like the (doubtful) presence of the *X* gene in avian hepadnavirus (Avihepadnavirus)[22,23], suggested an early split between these viral groups without cross-species transmission events between mammals and birds. The same can be proposed for the HBV found in primate, rodent and bat hosts where the observed divergence did not suggest interspecific transmission between mammals of different orders. On the other hand, transmission between closely-related species has been proposed for primate HBV.

Table 1 Mammals found with productive or resolved infection by hepatitis B virus

Taxa	Pos/Tot	HBV strain	Locality	Ref.
Order primates				
Family hominidae				
Pan paniscus	5/27		Captive	Heckel *et al*[43]
Pan troglodytes	11	chHBV	Wild caught and captive	Hu *et al*[40]
Pan troglodytes		gibIIHBV	Germany captive	Grethe *et al*[28]
Pan troglodytes	7/57		Captive	Heckel *et al*[43]
Pan troglodytes schweinfurthi	1/4	chHBV	East Africa	Vartanian *et al*[17]
Pan troglodytes troglodytes	6/62		Cameroon wild born	Lyons *et al*[21]
Pan troglodytes troglodytes	2/8	chHBV	Southwest Cameroon	Starkman *et al*[45]
Pan troglodytes troglodytes	1/46	chHBV	Wild Gabon	Makuwa *et al*[42]
Pan troglodytes troglodytes	7	chHBV	Congo, Cameron, Gabon wild	Makuwa *et al*[41]
Pan troglodytes vellerosus		chHBV	South-eastern Nigeria	Starkman *et al*[45]
Pan troglodytes verus	3	chHBV	Cameron wild born	MacDonald *et al*[29]
Pan troglodytes verus	1	chHBV	Gabon captive	Makuwa *et al*[41]
Pongo pygmaeus	8/38		Captive	Heckel *et al*[43]
Pongo pygmaeus	7/28		Taiwan captive	Huang *et al*[47]
Pongo pygmaeus	40/53	gibHBV	Thailand, prov. Ratchaburi, KhaoPratub Chang Wildlife Breeding Center	Sa-nguanmoo *et al*[78]
Pongo pygmaeus	83/195	gibHBV	Indonesia, E Kalimantan, W. Orangutan Reintroduction Center, captive and wild born	Warren *et al*[36]
Gorilla gorilla	2/11		Cameroon wild born	Lyons *et al*[21]
Gorilla gorilla	4/36		Captive	Heckel *et al*[43]
Gorilla gorilla	1	chHBV	Cameroon wild born	Grethe *et al*[28]
Family hylobatidae				
Hylobates lar	5/22		Paignton Zoo-captive born	Starkman *et al*[45]
Hylobates agilis			Taiwan	Starkman *et al*[45]
Nomascus gabriellae			Taiwan	Starkman *et al*[45]
Hylobates agilis	9/19	gibHBV	Taiwan captive	Huang *et al*[47]
Hylobates concolor	1	gibV HBV	Thailand, Duit	Grethe *et al*[28]
Hylobates concolor	2	gibIV HBV	Thailand, Duit	Grethe *et al*[28]
Hylobates concolor	4/7	gibHBV	North Vietnam and Central China	Noppornpanth *et al*[48]
Hylobates lar	3	gibIIHBV	Germany captive	Grethe *et al*[28]
Hylobates lar	1	gibIIIHBV	Thailand, Patas	Grethe *et al*[28]
Hylobates lar	3/10	gibHBV	Taiwan captive	Huang *et al*[47]
Hylobates lar	11/72	gibHBV	Thailand wild and captive born	Noppornpanth *et al*[48]
Hylobates lar	1/2		Bangkok, Dusit zoo	Sa-nguanmoo *et al*[78]
Hylobates leucogenys	1	gibIVHBV	Thailand, Duit	Grethe *et al*[28]
Hylobates leucogenys	1	gibVHBV	Vietnam, Cuc Phuong,	Grethe *et al*[28]
Hylobates moloch	1	gibIVHBV	Germany captive	Grethe *et al*[28]
Hylobates muelleri	1/3		Taiwan captive	Huang *et al*[47]
Hylobates pileatus	1	gibIIIHBV	France captive	Grethe *et al*[28]
Hylobates pileatus	12/20	gibHBV	Thailand wild and captive born	Noppornpanth *et al*[48]
Hylobates pileatus	2/6		Bangkok, Dusit zoo	Sa-nguanmoo *et al*[78]
Hylobates pileatus	At least 1	gibHBV		Huang *et al*[47]
Nomascus concolor	4/7		Thailand (originally from Vietnam and China)	Noppornpanth *et al*[48]
Nomascus gabiellae	1/1		Bangkok, Dusit zoo	Sa-nguanmoo *et al*[78]
Nomascus gabriellae	1/2	gibHBV	Taiwan captive	Huang *et al*[47]
Nomascus leucogenys	3/7	gibHBV	Taiwan captive	Huang *et al*[47]
Nomascus leucogenys	5/6	gibHBV	Bangkok, Dusit zoo	Sa-nguanmoo *et al*[78]
Family cercophitecidae				
Cercopithecus aethiops	1		Captive	Heckel *et al*[43]
Lophocebus albigena	1/5		Cameroon wild born	Lyons *et al*[21]
Macaca fascicularis	31/120	HBV genD	Mauritius Island (introduced)	Dupinay *et al*[54]
Mandrillus sphinx	2/9		Cameroon wild born	Lyons *et al*[21]
Papio ursinus orientalis	15/69	HBV genA2	S Africa, W, E Cape and Limpopo prov.	Dickens *et al*[51]
Family atelidae				
Lagothrix lagothricha	13/16	WMHBV	United States, Louisville Zoo. Garden captive	Lanford *et al*[56]
Order chiroptera				
Family vespertilionidae				
Subfam. miniopterinae				
Miniopterus fuliginosus	22	TBHBV	Kachin State, Myamar	He *et al*[24]
Family hipposideridae				
Hipposideros cf. ruber	4/51	HBHBV	Gabon	Drexler *et al*[26]
Family rhinolophidae				
Rhinolophus alcyone	1/16	RBHBV	Gabon	Drexler *et al*[26]
Family phillostomidae				
Subfam. sternodermatinae				

Uroderma bilobatum	5/54	TBHBV	Panama	Drexler *et al*[26]
Order rodentia				
Family sciuridae				
Marmota monax		WHV	United States captive	Summers *et al*[67]
Otospermophilus beecheyi		GSHV	United States, California	Marion *et al*[71]
Spermophilus parryi kennicot		ASHV	United States, Alaska	Testut *et al*[72]
Sciurus carolinensis pennsylvanicus		THBV	United States, Philadelphia	Feitelson *et al*[74]
Domestic animals				
Gallus gallus domesticus	37/129	Human HBV	China, Beijing	Tian *et al*[59]
Sus scrofa	266/416		China, Beijing	Li *et al*[18]
Sus scrofa	3	Human HBV	Brazil	Vieira *et al*[60]

HBV: Hepatitis B virus; Pos/Tot: Number of HBV positive animals/total number of animals analyzed for the presence of HBV infection; ASHV: Arctic squirrel HBV; BtHV: Bat (*Miniopterus fuliginosus*) hepatitis viruses; chHBV: Chimpanzee HBV; GSHV: Californian ground squirrel HBV; gibHBV: Gibbon HBV; HBV genA: Human HBV genotype A; HBHBV: Horseshoe bat HBV; RBHBV: Roundleaf bat HBV; TBHBV: Tent-making bat HBV; THBV: Tree squirrel HBV; WHV: Woodchuck HBV; WMHBV: Woolly monkey HBV.

Comprehensive phylogenetic analyses including avihepadnaviruses and orthohepadnaviruses clearly showed a high divergence at the nucleotide level between these two groups[24-26]. These analyses also revealed three groups of mammalian HBV, each associated with a different mammalian order: Rodentia, Chiroptera and Primates.

HBV infection in old world primates

Active and resolved HBV infections have been found in several species belonging to the genera *Pan*, *Gorilla*, *Hylobates*, *Nomascus* and *Pongo*[17,27-29]. Prevalence of infection in these animals is comparable to those found among humans in endemic areas[21]. Specific HBV strains were found in gorillas[30], chimpanzees[31] and gibbons[27,28]. Recent findings showed occurrence of recombination between HBV strains of human and chimpanzee[32], human and gibbon[33], and gorilla and chimpanzee[21], confirming the ability of HBV to cross species barriers. These findings suggested that transmission from humans to nonhuman primates or *vice-versa* were likely to occur wherever their habitats overlap.

Orangutans are apes of the Hominidea family with two extant species, *Pongo pygmaeus* and *Pongo abelii* (Figure 1). They are the only great apes found outside Africa, in the islands of Borneo and Sumatra[34]. Orangutans are highly endangered as a result of poaching and widespread destruction of their habitats resulting from human intrusions in their rainforest habitat. The accumulation of relatively solitary orangutans in reintroduction centers also increases the potential of transmission of viral pathogens, either of orangutan or human origin. Previous studies have shown the role of *Pongo pygmaeus* as an HBV host[35,36], carrying a specific HBV strain[30] and with individuals potentially becoming chronic HBV carriers[33]. In some places, prevalence of HBV in orangutans was as high as 59%, with 10% of them representing chronic carriers[35].

Chimpanzees are apes of the Hominidea family comprising two extant species, the gracile chimpanzee or bonobo (*Pan paniscus*), and the robust or common chimpanzee *Pan troglodytes* (*P. troglodytes*) with four subspecies: the western common chimpanzee (*P. troglodytes verus*), the central common chimpanzee (*P. troglodytes troglodytes*), the eastern common chimpanzee (*P. troglodytes schweinfurthii*), and *P. troglodytes vellerosus* (Figure 1)[37-39]. Wild chimpanzees still dwell in several forested regions of the lowest latitudes of sub-Saharan Africa[39]. This species has been the primary experimental model of HBV infection and they host indigenous nonhuman primate HBV strains[40]. Viral infection is widespread throughout the entire range of chimpanzee habitats; all four subspecies being infected with HBV-like viruses, collectively termed chHBV[17,20,28,29,31]. Strong associations between chHBV strains and their host geographic distribution have been found[20,41]. Chronic HBV infections usually result from perinatal infection and the presence of chHBV sequences in wild newborn chimpanzees suggests that natural perinatal transmission is responsible for their infection[40]. The finding of HBV in fecal samples collected from wild *P. t. troglodytes* showed that HBV detected in captive apes were related to viruses circulating in the wild[42]. Contacts between human and chimpanzees *via* the bushmeat trade, as family pets and caretakers, together with the number of viruses harbored by chimpanzees, pointed that these animals constitute putative reservoirs of infectious agents[17]. High prevalence rates of chHBV, of up to 25% in some wild communities (Table 1), further enhances the risk of cross-species transmission events.

Gorillas are apes of the Hominidae family belonging to the genus *Gorilla* comprising two species: *Gorilla beringei* with two subspecies (*G. b. beringei and G. b. graueri*), and *Gorilla gorilla* with two subspecies (*G. g. gorilla* and *G. g. diehli*)[37]. Gorillas are ground dwelling, predominantly herbivorous apes inhabiting the tropical or subtropical forests of central Africa (Figure 1). Evidence of past HBV infection was found in 11% to 30% of tested gorillas[43,44], none of which reported with current infection. Until now, only one western lowland gorilla (*Gorilla gorilla gorilla*) from Cameron has been reported with an HBV-like infection[28]. Whether this gorilla HBV sequence differed from that of chimpanzee HBV has remained unknown although some studies showed their close relationship[28,42,45]. The last authors suggested that sympatry of these two primate taxa, in the forests of west Africa, makes the possibility of cross-species transmission likely[42].

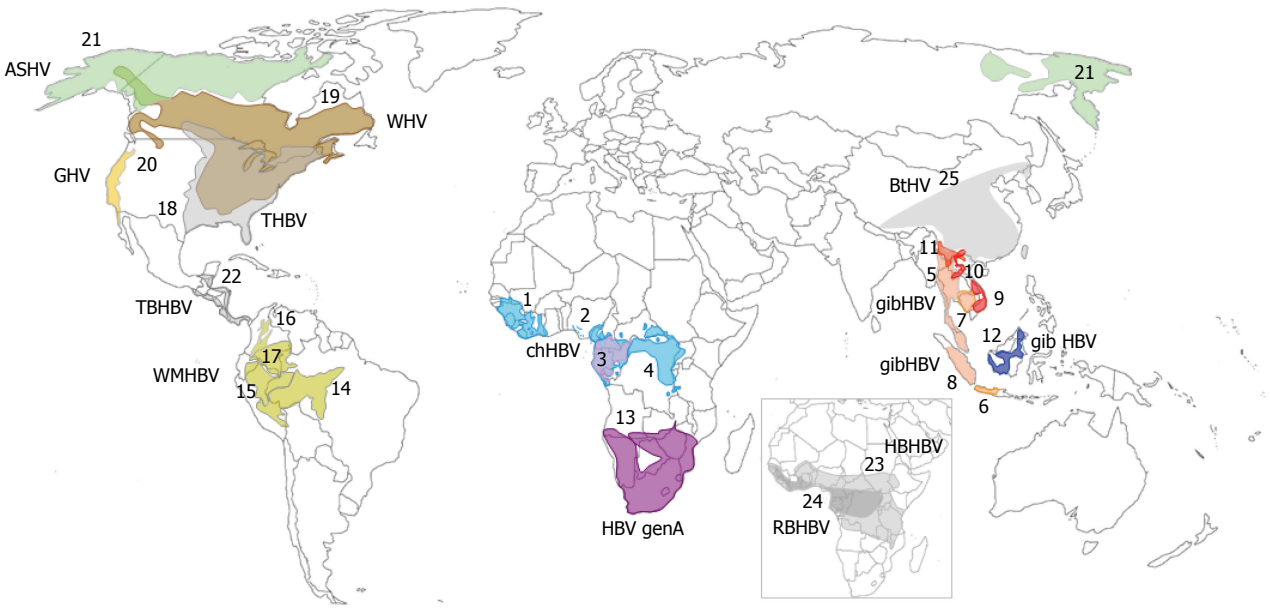

Figure 1 Geographic distribution of hepatitis B virus hosts. Primates: 1: *Pan troglodytes verus*; 2: *P. t. vellerosus*; 3: *P. t. troglodytes* and *Gorilla gorilla gorilla*; 4: *P. t. schweinfurthii*; 5: *Hylobates lar*; 6: *Hylobates moloch*; 7: *Hylobates pileatus*; 8: *Hylobates agilis*; 9: *Nomascus gabriellae*; 10: *Nomascus leucogenys*; 11: *Nomascus concolor*; 12: *Pongo pygmaeus*; 13: *Papio ursinus*; 14: *Lagothrix cana*; 15: *Lagothrix poeppigii*; 16: *Lagothrix lugens*; 17: *Lagothrix lagothricha*. RODENTIA: 18: *Sciurus carolinensis*; 19: *Marmora monax*; 20: *Otospermophilus beecheyi*; 21: *Spermophilus parryii*. Chiroptera: 22: *Uroderma bilobatum* (partial distribution); 23: *Hipposideros ruber*; 24: *Rhinolophus alcyone*; 25: *Miniopterus fuliginosus*. HBV: Hepatitis B virus; ASHV: Arctic squirrel HBV; BtHV: Bat (*Miniopterus fuliginosus*) hepatitis viruses; chHBV: Chimpanzee HBV; GSHV: Californian ground squirrel HBV; gibHBV: Gibbon HBV; HBV genA: Human HBV genotype A; HBHBV: Horseshoe bat HBV; RBHBV: Roundleaf bat HBV; TBHBV: Tent-making bat HBV; THBV: Tree squirrel HBV; WHV: Woodchuck HBV; WMHBV: Woolly monkey HBV.

Gibbons are lesser apes belonging to the Hylobatidae family, comprising four genera, *Hylobates, Nomascus, Hoolock,* and *Symphalangus*, and distributed in tropical and subtropical rainforests from northeast India to Indonesia and northern to southern China, and the islands of Sumatra, Borneo and Java (Figure 1)[46]. Phylogenetic analysis of complete HBV surface (S) gene sequences revealed that gibbon viruses clustered separately from hepadnaviruses of other hosts[48]. Several species of *Hylobates* and *Nomascus* were found to be infected by at least four different HBV strains[28,33,47]. An HBV isolate from a *Nomascus leucogenys* found in Thailand was phylogenetically separate from those found in *Hylobates pileatus* and *Hylobates lar*, and was almost identical with an HBV isolate from *Hylobates concolor*, confirming the circulation of several HBV strains in gibbons[29]. Evidence for horizontal and vertical transmission in captive gibbons was been found, and HBV DNA has also been detected in the saliva of gibbon HBV carriers[48]. Some gibbon species have been shown to become chronic HBV carriers[33]. A previous study showed a high prevalence (ca. 41%) of infection by HBV in captive and possible horizontal transmission between infected gibbons in Taiwan[47]. In this study, saliva samples of HBV carrier gibbons tested positive for HBV DNA, demonstrating a potential infection through contact with bodily fluids.

Phylogenies based on complete HBV genome sequences of different primate species suggest that interspecific transmissions might take place between man and closely-related genera (*Pan*, *Gorilla*, *Pongo*, and *Hylobates*). This can be deduced from the grouping of HBV genotypes found in the great apes with human specific HBV genotypes. However, analyses carried out with different HBV genomic regions showed a more complex picture, where recombination events between genotypes were demonstrated[19,21,30].

Recombination events between human HBV genotypes are frequently reported and some sub-genotypes clearly result from recombination events between different genotypes[49]. These events were also hypothesized as part of the evolutionary history of HBV genotypes from *Homo sapiens*, *Pan*, *Gorilla*, *Pongo* and *Hylobates*. In these cases, there is evidence that recombination has been a relevant process[21] although it is not clear whether recombination events occurred before or after the initial infection in each species. An interesting case was reported by Tatematsu *et al*[13], showing that the new human genotype J found in one patient resulted from a recombination event between human HBV/C and gibbon HBV. No other man or gibbon was found infected by this virus. Zhou and Homes[50], analyzing recombination events with different algorithms, suggested that recombination between HBV genotypes more frequently occurs between the positions 1627 and 3252. Lyons *et al*[21], who analyzed recombination between human HBV genotypes and between great ape HBV genotypes, found similar results and showed evidence that recombination has recurrently taken place during evolution of HBV genotypes.

Baboons are social monkeys of the Cercopithecidae family, with five *Papio* species commonly recognized despite controversies on their *bona fide* status as valid species or subspecies. These comprise *Papio ursinus*, or the

chacma baboon (Figure 1), *Papio papio*, or the Guinean baboon, *Papio hamadryas*, or the hamadryas baboon, *Papio anubis*, or the olive baboon, and *Papio cynocephalus*, or the yellow baboon. The practice of daily grooming with several related and unrelated individuals, including offspring, indicate that horizontal baboon-to-baboon transmission of HBV has been likely, and the well-documented interactions between humans and baboon make cross-species transmission of this virus plausible[51]. Despite previous hypothesis of a lack of susceptibility of baboon to HBV infection[52], later studies showed that *Papio ursinus orientalis* was capable of been infected with HBV[53]. More recently, *Papio ursinus* liver samples from specimens caught in South Africa were found to be naturally infected with HBV DNA subgenotype A2, with evidence of lifelong persistence of this virus and occurrence of occult HBV infections[51]. The overall prevalence (21.7%) of HBV in baboons has been found to be similar to other nonhuman primates in areas to which HBV is highly endemic[33,51].

Dupinay *et al*[54] detected the presence of the human HBV sub-genotype D3 in serum and liver samples of *Macaca fascicularis* from the Mauritius Islands. HBV DNA prevalence of 25% in serum samples of 120 specimens and 42% of liver samples from 50 specimens was reported.

These reports described the likely occurrence of HBV transmission from humans to monkeys demonstrated by similarities between HVB isolates from these species and human sub-genotypes, accounting for 98% for *Macaca fascicularis* and HBV/D3, and 99% for *Papio ursinus orientalis* and HBV/A2. Interestingly, although the *Papio/Macaca* lineage split from *Homo/Pan/Gorilla/Hylobates* ca. 30 million years ago[55], *Papio ursinus orientalis* and *Macaca fascicularis* have been capable of maintain a chronic or occult infection caused by a human HBV virus lineage.

HBV infection in neotropical primates

Wooly monkeys belong to the *Lagothrix* genus, a neotropical primate taxon of the Atelidae family. *Lagothrix* comprises at least four species: *Lagothrix lagotricha*, *Lagothrix poeppigii*, *Lagothrix lugens*, and *Lagothrix cana* (Figure 1). They are the only neotropical monkeys found to host a specific HBV[56]; 81% (13/16) of animals from the Louisville Zoo colony showed signs of ongoing or previous infections with wooly monkey HBV (WMHBV). Nine polymerase chain reaction (PCR)-positive animals showed consistent profiles with either acute or chronic infection. PCR analysis of archived sera showed that many infections were chronic and had been present in the colony for at least 9 years prior to the study[56]. Data of WMHBV infections in the Louisville colony were consistent with vertical transmission. At the time of that study, *Lagothrix* was considered to be a monotypic genus with a single species *L. lagothricha*. The current taxonomic arrangement splitting *L. lagothricha* in four species does not allow us to know which species was identified as the HBV reservoir.

WMHBV is the only HBV so far described in neotropical primates and was only detected in captive animals[57]. The WMHBV genome is capable of replicating and producing virions in human liver cell lines but experimental infection using the spider monkey (*Ateles geoffroyi*) as a model did not result in permanent infection, with viral clearance 16 wk after infection[57]. Phylogenetic analyses showed that WMHBV divergence occurred before the radiation of the remaining primate HBV genotypes, with a nucleotide sequence similarity ranging from 62% to 86% in different open reading frames between different genotypes. WMHBV was not detected in wild specimens, a reason why it is unclear whether this HBV might actually infect wild populations of wooly monkeys.

HBV infection in domestic animals

Research on HBV-like viruses in domestic animals has been carried out since 1985[58]. Recently, liver of captive swine and chickens were found to be naturally infected with HBV in China[18,59]. These findings, together with the known ability of HBV to cross species barriers[19], suggested that human and nonhuman HBV variants might share hosts in nature. Recently, serological data from several samples from swine from Brazil and partial genome sequencing (252-365 bp) of three of these samples confirmed HBV infection, with sequences sharing 93%-96% of identity with human HBV[60]. Although there is no evidence that human populations have been so far infected with HBV variants of animals used for food, animal source foods deserve a closer attention[59].

HBV infection in bats

Bats (order Chiroptera) are a source of a wide variety of emerging pathogens, including coronaviruses, filoviruses, Hendra and Nipah paramixoviroses, lyssaviruses and HBV[61]. A recent study provided strong evidence of circulation of orthohepadnaviruses in *Miniopterus fuliginosus* bats from Myanmar[24]. *Miniopterus fuliginosus* was initially considered a junior synonymous of *M. schreibersii*, but molecular studies inferred from mitochondrial cytochrome *b* sequences showed that *M. fuliginosus* was a valid species[62]. The virus found in this bat species differed from currently known members of the genus Orthohepadnavirus, representing a new species. Prevalence of bat hepatitis viruses in *Miniopterus fuliginosus* from two localities was 2.2% and 4.7%, respectively, indicating that this species was likely a natural reservoir of BtHV[24]. These bats are widely spread and host other viruses, including coronaviruses and betaherpesviruses[63-65].

A screening of 3080 bat specimens belonging to 54 species and 11 families showed ten specimens (0.3%) from Panama and Gabon carrying unique hepadnaviruses in co-ancestral relation to HBV, putatively classified as orthohepadnavirus species[26]. Infected livers showed histopathologic alterations compatible with hepatitis. Phylogenetic analyses carried out with generated virus sequences suggested that bat HBV was more closely-related to primate HBV than to those of other mammalian orders.

HBV infection in rodents

Woodchuck (*Marmota monax*), a rodent of the Sciuridae

family, is distributed in Canada and United States, including Alaska (Figure 1)[66]. This species is common and territorial, with highly variable densities ranging from 0.1 to 3.3/hectare and with loosely structured populations in burrow systems without spatial clusters[66]. Viruses similar to HBV were found in a laboratory population of woodchucks and designated woodchuck hepatitis virus (WHV)[67]. Subsequently, WHV was found in a natural population of woodchucks from southeastern Pennsylvania, central New Jersey, and north central Maryland[68].

Spermophilus beecheyi, currently known as *Otospermophilus beecheyi* (ground squirrel), is a rodent of the Sciuridae family distributed in United States and Mexico (Figure 1)[69,70]. This species lives in rocky habitats and is widespread and locally abundant in most of its habitats, including agricultural areas, but can be rare in other places[70]. The ground squirrel hepatitis virus shared many of the unique characteristics of HBV, and has been found in Beechey ground squirrels of northern California[71].

Spermophilus parryii kennicottii, currently known as *Urocitellus parryii kennicottii* (arctic ground squirrel), is a rodent of the Sciuridae family. *Urocitellus parryii* is distributed in Canada, Alaska in United States, and Russia (Figure 1)[70]. This species lives in colonies with complex system of shallow burrows (up to 1 m) with several entrances and nests[69]. Testut *et al*[72] found that 14% of the 56 analyzed animals were positive for ASHB (artic ground squirrel HBV).

The tree squirrel *Sciurus carolinensis*, a rodent of the Sciuridae family, occurs in United States and Canada (Figure 1), while *S. c. pennsylvanicus* occurs in the northeast of this distribution[73]. Based on histological evidence of hepatitis in 14 of 94 samples of tree squirrel livers, DNA polymerase and cross-reactive surface antigen activities in 3 of 14 livers, a virus similar to, but different from HBV was identified, named tree squirrel hepatitis B virus (THBV)[74].

CONCLUSION

Several hypotheses have been postulated to explain the origin and evolution of HBV. The manyfold genotypes found in humans might have originated by multiple episodes of zoonotic transmissions from several nonhuman primate species[29]. This hypothesis is similar to the one proposed by the human immunodeficiency virus (HIV) type 1 from at least four separate cross-species transmission from different subspecies of chimpanzees or gorillas[75,76] while human infection with HIV type 2 in west Africa arose independently through contact with sooty mangabeys[77]. Like for HIV, the constant and increasingly frequent exposure of humans to blood, meat and bodily fluids of infected wild and domestic animals during poaching and meat processing and preparation provides a recurrent source of cross-species transmission events of HBV-like viruses to humans. Such events might be even more frequent than perceived, since only a small fraction of cross-species transmitted viruses is thought to culminate with successful establishment of infection leading to virus replication and pathogenesis. The higher physical stability of HBV-like viruses (*e.g.*, compared to HIV)[78] may enhance such scenario of successful establishments in the human host.

The dynamic interplay between the host and the virus depends on viral facts such as viral genetic variation and viral genotype[25]. The increase in reports on the circulation of HBV in different species of mammals and birds has stimulated interest in identifying new reservoirs and genotypes, indicating the need for additional studies to a greater understanding of the dynamics of transmission of HBV to humans and other species susceptible to the virus. Although transmission of human hepatitis B virus variants to nonhuman primates is well documented, it remains to be elucidated whether nonhuman primate HBV and those from other vertebrate species are transmissible to man.

ACKNOWLEDGMENTS

We would like to thank Dr. Héctor N. Seuánez for reviewing the draft version of the manuscript.

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P- Reviewers: Guo JS, Wilhelm B **S- Editor**: Zhai HH
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ISSN 1007-9327