Genetic Diversity of the Hepatitis B Virus and Its Epidemiological Significance

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4.1 Genotypes, Subgenotypes, and Serological Subtypes of Hepatitis B Virus

In the 1970s of the last century, nine different serological subtypes (serotypes) of HBsAg (ayw1, ayw2, ayw3, ayw4, ayr, adw2, adw4, adrq−, adrq+) were identified in a number of studies using monoclonal antibodies [1–3]. This HBsAg subtype classification has been applied to investigate the geographical distribution of HBV variants [4]. Further studies have shown that the subtypes of HBsAg do not reflect the true genetic diversity of HBV [5]. As the classification was based on a limited number of amino acid substitutions, in some cases, the subtype of HBsAg could change as a result of only one point mutation in the gene that encodes this protein. Thus, two amino acids encoded by the 122 and 160 S-gene codons determined the HBsAg's assignment to d/y and w/r subtypes, respectively [6–8]. By 1988, the complete genomes of 18 HBV strains of various subtypes were sequenced, which paved the way for the development of the first genetic classification of HBV. Okamoto et al. originally divided the available isolates of HBV into four genetic groups designated A, B, C, and D [8]. Two new groups, designated E and F, were identified based on S-gene variability of ayw4 and ayd4 subtypes [9, 10]. Later, three more

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genotypes of HBV (G, H, and I) were described [11–13]. Recently, a tentative genotype J strain was reported and isolated from a single individual in Japan [14]. Current HBV genotype classification is based on intergroup divergence greater than 7.5% in phylogenetic analysis. Genotypes A, B, C, D, F, and I are further classified into subgenotypes-subgroups with nucleotide divergence between 4% and 7.5% and high phylogenetic bootstrap support [15, 16] (Fig. 4.1).

For genotype A four subgenotypes, A1, A2, A3, and A4, were described [16–18]; however, subgenotype A3 is often referred to as quasi-subgenotype because it does not meet the criteria for subgenotype classification [19]. Previously misclassified subgenotypes A5 and A7 belong to subgenotype A4, and A6 belongs to subgenotype A3 [19]. Genotype B is divided to five subgenotypes [16, 20, 21]. Comprehensive analysis of genotype B has led to the reclassification of several subgenotypes: strains preliminary assigned to B5, B7, B8, and B9 were defined as subgenotype B3, and subgenotype B6 was reclassified to B5 [19, 22]. Within genotype C subgenotypes C1–C5 are well characterized [16, 23]. Eleven new genetic variants of HBV, designated as subgenotypes C6–C16, have recently been described in a series of studies from Southeast Asia [24–28]. Later, some strains of subgenotype C14 were reclassified to subgenotype C2 [19]. Genotype D is divided into six subgenotypes, D1–D6 [22]; however, its classification is still disputable. Previously described subgenotypes D7–D9 were found to be recombinant genetic variants [19, 28–30]. The nucleotide divergence between D1 and D3 strains is less than 4%,

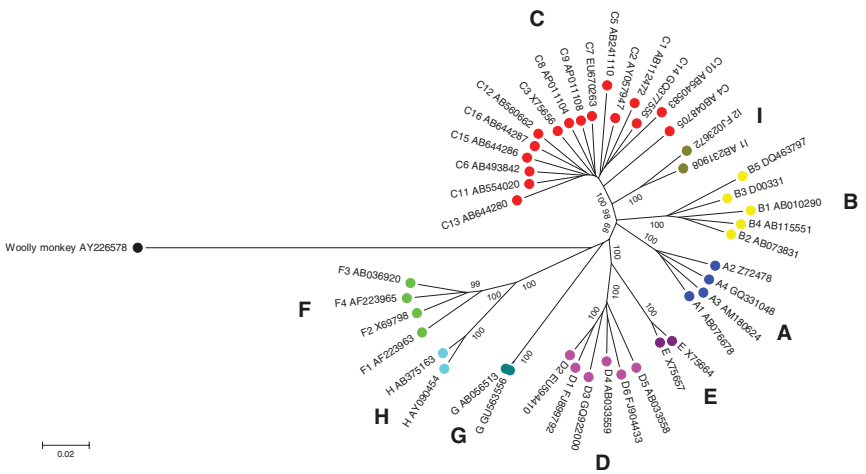

Fig. 4.1 Phylogenetic relationships of HBV genotypes and subgenotypes. The tree was constructed by the neighbor-joining method. The evolutionary distances were computed using the maximum composite likelihood method. Bootstrap analysis values greater than 95% are shown. The analysis involved 44 full-length HBV genomes from GenBank. Subgenotype and accession numbers are shown in taxa names. Woolly monkey strain was used as an out-group. Evolutionary analyses were conducted in MEGA7 software

and subgenotypes D4–D6 also show signs of intergenotype recombination [19]. Genotype F was originally divided into two subgenotypes, F1 and F2 [16], and in subsequent studies, two new genetic variants, subgenotypes F3 and F4, were identified [31, 32]. Genotype I strains identified so far are shown to be recombinants of unknown genotype (first part of the genome) and genotype C (second part of the genome from 1600 to 3000 bp). However, extensive analysis of their genetic and phenotypic characteristics agreed to group these variants into a separate genotype [13, 33]. Two subgenotypes I1 and I2 deviate less than 4% from each other; however, they belong to different subtypes (adw2 and ayw2), thus can be distinguished as unique subgroups [33].

4.2 Geographical Distribution of HBV Genotypes and Subgenotypes

HBV genotypes and subgenotypes show characteristic geographical distribution (Fig. 4.2). Genotypes A and D have been found throughout the world, although in some regions, they have higher prevalence and their subgenotypes often have distinct distribution.

Genotype A circulates in Europe, Africa, and the Americas. Subgenotype A1 prevails in countries of Southern and Eastern Africa, Southern Asia, and South America [16, 34, 35]. It was hypothesized that it originally was exported from Africa with a slave trade [22]. Subgenotype A2 is found mainly in Europe and North

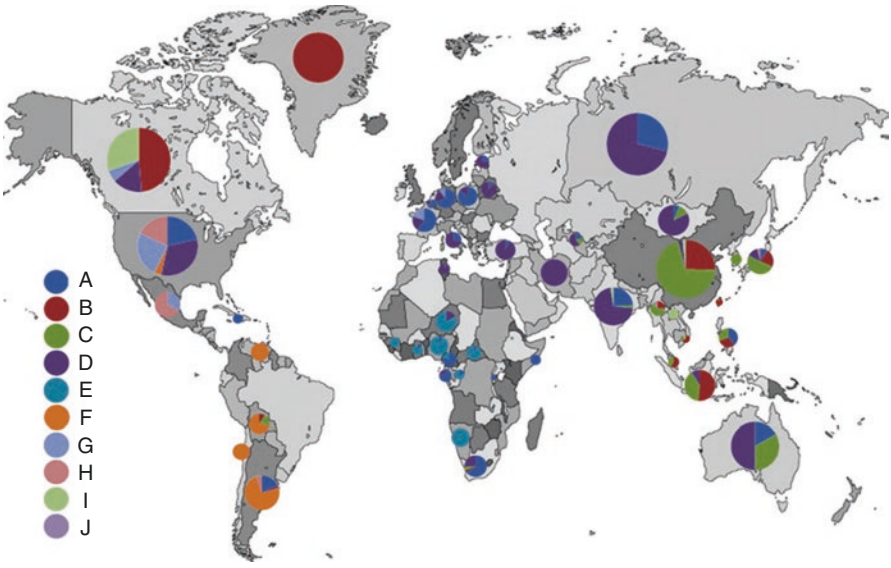

Fig. 4.2 Geographic distribution of HBV genotypes. Source: Shi W. et al. Infect Genet Evol 2013; 16:355–361

America [16, 22]. Subgenotype A3 is isolated in patients from Cameroon, Gabon, Rwanda, and Nigeria and from African population of Haiti [17, 18, 36, 37]. Subgenotype A4 is also found in Africa (Mali, Cambia, Congo, Rwanda) [18, 38].

Genotypes B and C are common in Asia. Subgenotype B1 is found predominantly in Japan; B2 in China; B3 in Indonesia, Philippines, and China; B4 in Vietnam and Cambodia; and B5 in Inuits of Arctic region [20, 21, 24, 39]. Subgenotype C1 prevails in Mainland Southeast Asia, C2 is mostly from East Asia, C3 is predominant in Oceania, C4 is exclusively found in aborigines from Australia, and subgenotypes C5–C16 circulate in Indonesia and Philippines [16, 24, 25, 28, 40, 41].

Genotype D is the second most common genotype and dominates in Mediterranean countries, India, Eastern Europe, and North America [16, 42, 43]. Subgenotypes D1–D3 cocirculate in many parts of the world. D1 is the most common in Mediterranean region (Greece, Turkey, North Africa), Russia, Iran, and Pakistan [16, 44, 45]; D2 in Eastern Europe and Turkey [16, 46]; and D3 in Canada, Alaska, and Russia [45, 47, 48]. Subgenotype D4 was found in aboriginal population of Papua New Guinea and Australia [10], D5 in some Indian tribes [49], and D6 in Indonesia [28].

Genotype E prevails in West Africa [50]. Genotype F is distributed in South and Central America, as well as in Alaska. Subgenotype F1 was found in Argentina, Chile, Costa Rica, Salvador, and Alaska; F2 in Venezuela and Brazil; F3 in Columbia, Panama, and Venezuela; and F4 in Brazil, Argentina, and Bolivia [51]. Genotype G is reported from Central and North America, as well as from Europe [11, 52, 53]. Genotype H was mostly found in Central America and Mexico [12, 52]. Both subgenotypes of genotype I (I1 and I2) are found in Laos and Vietnam. I1 strains were also reported from China and I2 from some Indian tribes. Geographical distribution of the main genotypes, subgenotypes, and serotypes is presented in Table 4.1.

Migratory processes that are gaining strength with each passing year lead to a gradual erasure of clear boundaries of the geographical spread of certain genotypes. In a large-scale study that included 17 hepatological centers in the United States, 7 HBV genotypes were registered: A (33%), B (21%), C (34%), D (9%), E (1%), F (1%), and G (1%). A reliable relationship between race and genotype of HBV was revealed. Thus, genotype A was detected in Caucasians and African Americans, while genotypes B and C prevailed among Asians. In Americans, born in the United States, Europe, the Far East, and Southeast Asia, the most common HBV genotypes were A, D, C, and B, respectively [54].

4.3 HBV Genotypes and Vaccination

The most widespread recombinant HBV vaccine is derived from subgenotype A2 that is found predominantly in Europe and North America [55]. The early research demonstrated cross-protection between HBsAg subtypes in chimpanzees [56, 57] as well as in a field studies [58]. Although global experience suggests that there is a high degree of cross-protection among the subtypes of the virus, there is convincing

Table 4.1 Geographical distribution of HBV genotypes, subgenotypes, and subtypes

Genotype	Subgenotype	Serological subtype	Geographic distribution
A	A1	adw2/ayw2	Africa
	A2	adw2	Europe/North America
	A3	ayw1	Africa, Haiti
	A4	ayw1	Africa
B	B1	adw2	Japan
	B2	adw2	China
	B3	adw2	Indonesia, Philippines, China
	B4	ayw1/adw2	Vietnam, Cambodia, France
	B5	adw2	Eskimos/Inuits
C	C1	adr	Thailand, Myanmar, Vietnam
	C2	adr	Japan, China, Korea
	C3	adr	New Caledonia, Polynesia
	C4	ayw2/ayw3	Australian aborigines
	C5	adw2	Philippines, Indonesia
	C6–C12	adr	Indonesia, Philippines
	C13–C15	adr	Indonesia
	C16	ayr	Indonesia
D	D1	ayw2	Middle East, Central Asia
	D2	ayw3	Europe, Japan, Lebanon
	D3	ayw2/ayw3	Worldwide
	D4	ayw2	Australian aborigines, Micronesians, Papua New Guineans, Arctic Denes
	D5	ayw3/ayw2	India
	D6	ayw2	Tunisia, Nigeria
E	–	ayw4	Western/Central Africa
F	F1	adw4	Argentina, Costa Rica, El Salvador, Alaska
	F2	adw4	Nicaragua, Venezuela, Brazil
	F3	adw4	Venezuela, Colombia
	F4	adw4	Argentina
G	–	adw2	USA, Mexico, Germany, Italy, UK, France
H	–	adw4	Mexico, Japan, Nicaragua, USA
I	I1	adw2	Laos, Vietnam, China
	I2	ayw2	Laos, India, Vietnam

Modified from: Kramvis A. Intervirology, 2014; 57:141–150

evidence that protection between homologous variants of HBV is much stronger than between heterologous variants. Two well-documented cases of acute and chronic hepatitis B caused by HBV genotype F in fully vaccinated individuals with protective titers of antibodies have been described in Europe [59, 60]. In a large-scale study among 2.13 million US blood donors, nine cases of occult (HBV DNA positive, anti-HBc negative) HBV infection were identified. In three cases of non-vaccinated individuals, HBV genotype A only was found; however, in the majority of vaccinated cases, non-A genotypes prevailed (five out of six cases) [61]. All these vaccinated donors remained asymptomatic but were HBV DNA positive for several weeks before the infection was resolved. In the cohort of 2028 vaccinated Chinese blood donors, 24 cases of HBsAg-negative HBV DNA-positive cases were found.

Among 15 cases with known HBV genotype, 14 had genotype B and 1 genotype C [62]. None of the described above breakthrough infections in vaccinated individuals were caused by vaccine escape mutants, but almost all had HBV genotype heterologous to vaccine strain. Available data suggests that symptomatic HBV infection after successful vaccination is a rare event; however, asymptomatic transient infection is quite frequent, and protection depends on HBV genotypes [55, 63].

4.4 HBV Genotypes and Transmission Route

The way of transmission of HBV infection depends on many factors: prevalence of HBV in the region, level of socioeconomic development of the country, cultural and ethnic characteristics, lifestyle, occupation, HIV co-infection, etc. In highly endemic regions, such as Southeast Asia, the most common route is a mother-to-child transmission. It is well known that genotypes B and C prevail in these regions [22]. The most significant association with mother-to-child transmission is revealed for HBV genotype C [64]. It is possible that the highest genetic heterogeneity of genotype C (16 subgenotypes) is in part a consequence of the evolution of the virus under the dominant transmission route. For Europe, where genotypes A and D predominate, sexual and nosocomial routes of HBV transmission are the most significant. By penetrating into the risk groups, certain HBV genetic variants can get predominant spread within these populations. Thus, there are reports of transmission of HBV genotypes A and G among men who have sex with men (MSM) [53, 65, 66]. The predominant distribution of the genotype D (mainly subgenotype D3) is described in acute hepatitis B among people who inject drugs (PWID) in Canada, where this genotype is less prevalent in general population [67]. Interestingly, the connection of subgenotype D3 to transmission with drug use and unsafe injections, in contrast to the subgenotype A2, for which sexual transmission was more characteristic, was also reported from Europe [68–71]. Another example of association between route of transmission and genotype is a report from Argentina where two simultaneous epidemics were identified: one among PWID caused by genotype A and the other among MSM caused by genotype F [72]. The data on association between particular transmission routes and HBV genetic variants can be useful in an epidemiological investigation [73]. From the evolutionary point of view, the route of transmission can be an important factor influencing the rate of genetic changes and, thus, facilitating the acquisition of new phenotypic properties by HBV genotypes.

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