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REVIEW ARTICLE

Hepatitis B Virus Molecular Characterization and Prevalent Genotypes in Iraq and Some Middle Eastern Countries

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ABSTRACT

Hepatitis B virus occurs among the ubiquitous viral pathogens that pose a serious threat to the lives of millions around the globe. As a consequence of lacking proofreading during the replication cycle directed by the reverse transcriptase, HBV became distinguished by a considerable genetic variation. To date, ten different genotypes of this virus have been recognized through our world. Each of these genotypes was linked to various rates of severity and disease outcomes, ranging from cirrhosis to liver carcinoma, and to response to antivirals as well. Therefore, genotypic studies and molecular characterization of the virus may offer unparalleled assistance to predict the most successful treatment approaches. Moreover, this review attempts to clarify some aspects of the HBV molecular biology and to provide an updated insight to genetic variations through collecting of the most recent or available studies by web searching engines conducted in several countries of the Middle East. Thus, it has been noted that the dominant genotype of HBV in several cities in Iraq as well as Middle Eastern regions was represented by genotype D (96.8% & 90%, respectively). However, other local studies showed considerable elevation in the rate of mixed infections, where the most frequent mixtures were composed of 3 and 2 genotypes represented by 35.1 and 29.7%, respectively.

INTRODUCTION

Viral hepatitis is a systemic disease involving the liver as the primary organ. Frequently, cases of viral hepatitis are attributed to one of the following viruses: Hepatitis A virus (infectious hepatitis/HAV); Hepatitis B virus (serum hepatitis/HBV); Hepatitis C virus (post-transfusion/HCV); Hepatitis D (co-infection dependent/ HDV); or Hepatitis E virus (HEV)[1]. Moreover, newly identified hepatitis causing viruses include Hepatitis F and Hepatitis G viruses, Transfusion Transmitted virus (TTV), and SEN virus as well. These infectious viruses affect and infect hepatocytes as the primary target. Although significantly may overlap in their clinical manifestation, yet they differ vastly in morphologic, genomic, and replicative characteristics[2,3].

Infections of Hepatitis B virus represent a global burden for the systems of public health, affecting nearly 350 million people worldwide. This burden is manifested by the high rates of morbidity and deaths subsequent to severe diseases like chronic hepatitis, hepatic failure, cirrhosis, and hepatocellular-carcinoma (HCC)[4,5]. Furthermore, HBV and HCV infections are associated with not less than 90% of all HCC incidences in the developing countries as compared to only 40% in developed ones, with HBV being the major contributor in 66% of the cases[6,7]. Despite being minimized through immunization efforts, viral Hepatitis B has caused about one million mortalities in 2020[8].

Hepatitis B Virus

Hepatitis B, the prototype member of the *Hepadnaviridae* family, is a hepatotropic and non-cytopathic virus. It initiates the infection by entering the hepatocytes via sodium-taurocholate cotransporting polypeptide (NTCP) receptor, and replicates via reverse transcribing of an intermediary RNA. Although not essential for replication, the viral DNA may integrate within the host genome, which potentially initiates hepato-carcinogenesis[9,10].

The genome of HBV is a circular partially double-stranded DNA, approximately 3200 base pairs. Also, the virally encoded reverse transcriptase (RT) that replicates DNA via an RNA intermediate lacks proof-reading capability which, in turn, leads to higher error frequencies[11]. However, variants of HBV arise due to persistent long-term infections and various selective pressures[12]. Despite the higher substitution rates in the HBV genome, ten genotypes and over thirty sub-genotypes were recognized based on nucleotide sequencing approaches. Also, several criteria guide the sub-genotype classification, including whole genome analysis, range of sequence divergence, strains specific motifs, as well as random reference sequences[13]. Thus, genotyping process is a crucial for establishing accurate correlations between genotypes and regional distribution, clinical outcomes, progression of the disease, and the response to antiviral therapies[14].

Furthermore, the genome of HBV encodes proteins via four partially-overlapping open reading frames (ORF) depicted in figure 1, and include: surface (preS/S), core (preC/C), polymerase (P) and X. The preC/C encode both e and c antigens (HBe/c Ag); P for polymerase; the S for three surface proteins [small (S), middle (M), and large (L) HBsAg] and X ORF for trans-activator X protein, which is involved in regulatory functions including signal transduction, apoptosis, and induction of hepato-carcinogenesis[15,16].

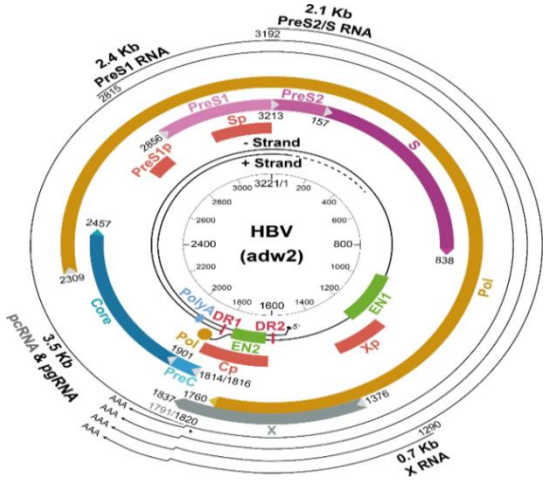

Figure 1: The genomic structure of the HBV. The shown locations include the regulatory elements (EN1 and EN2 enhancers), and the four promoters. The approximate sites for initiation of transcription of RNA, and the unique poly (A) site are also indicated with the locations of the four ORFs. The nucleotide length is based on the adw2 isolate of HBV (genotype A). Cp, core promoter; PreS1p, preS1 promoter; Sp, S promoter; Xp, and X promoter. Adapted from Chuang *et al*[15].

Like other viruses, HBV utilizes various strategies to enhance its evolutionary survival such as recombination and random mutations. However, the resulted mutants display uneven associations with disease severity. For instance, mutants with preS/S deletions and preC/C promoter mutations are linked to higher correlation with the HCC and risk of progressive liver damage[17].

Hepatitis B Virus Serotypes and Seroprevalence

Initially, HBsAg was classified into four serologic subtypes (adw, adr, ayw and ayr) relying on the immune-reactivity against limited number of amino acids in the envelope. This system, however, has been replaced by a more accurate classification based on whole genome sequencing[18]. Moreover, viral particles containing surface antigens are complex, each carrying group-specific antigen and two pairs of mutual sub-determinants (d/y or w/r), which gives rise to four phenotypic variants of HBsAg. These serologic markers are valuable in epidemiological studies, particularly in tracking secondary cases to the index case[1]. Additionally, these four probable combinations specify the major subtypes; with additional amino acids contribute to the immunogenicity. The four main sub-serotypes can be further divided into nine distinct serotypes (adw2, adw4q-, adr-q+, adr-q-, ayw1-4 and ayr)[19]. Also, a correlation exists between HBV genotype and HBsAg subtypes. For example, genotypes A, B, F & G are associated to the subtype adw, while HBV/D or E genotypes typically express serotype ayw[20].

The seroprevalence of HBV infection varies by country and population groups. HBV is an endemic disease in Iraq, with prevalence rate of 1 to 3.5% according to region[21]. One study among Iraqi blood donors reported 71% seropositivity for HBsAg[22]. Another study reported a rate of 49% seropositivity in thalassemia and kidney failure patients[23]. Although serologic testing is the widely utilized for screening, nevertheless misdiagnosis may occur as real-time PCR confirmation revealed discrepancies in about 29% of cases[24]. However, some inconsistencies may occasionally be encountered with immunologic and molecular studies, particularly with viral studies[25]. In neighboring countries, HBV prevalence varies: 1.3% in Saudi Arabia[26], 2.3% among Syrian refugees in Turkey[27], 2.4% in Jordan28, and 1.4% in Egyptian population[29].

Hepatitis B Virus genotypes:

Hepatitis B has been subdivided into a various genotypes based on genome sequencing. To date, ten genotype variants (A-J) of the genome have been characterized. Moreover, some genotypes have been further classified to sub-genotypes. To be qualified as a distinct genotype, the genome sequence must exhibit more than 8% variation, and a divergence of 4-8% is required for scoring sub-genotypes. Based on the above-mentioned criteria, over 30 sub-genotypes of HBV have been recognized[30,31]. Concerning the prevalent genotypes, studies conducted in the Middle Eastern countries have consistently shown genotype D as the most regionally prevalent HBV genotype. The summarized findings of these studies are presented in Table 1.

Furthermore, the findings of those researchers align with studies conducted across various provinces and cities in Iraq, which have also identified HBV/D as the predominant genotype, accounting for 96% of the detected genotypes. Other genotypes including C, A, and B, have also been detected and as presented in Table 2.

However, other local Iraqi studies conducted in different regions by using nested-multiplex PCR techniques revealed that many HBV infections involved mixed genotype. Notably, the mixed infections involving two and three genotypes were frequently observed, accounting for approximately 30% and 35% of cases, respectively as shown in Table 3.

Table1: The distribution of HBV genotypes in some countries of the Middle East.

Country	Genotype	%	Average%
Bahrain[32]	D	61	D= 90
	A	10	
Egypt[33]	C	60	C= 5.17
	D	40	
Gaza (Palestine)[34]	D	100	A= 3.96
Iran[35]	D	100	
Iraq[36,37]	D	100	E= 0.9
Jordan[38]	D	100	Total= 100%
Saudi Arabia[39]	D	90	
	E	10	
Turkey[40]	D	98	
Lebanon[41]	D	100	
Oman[42]	D	76	
	A	18	
Syria[43]	D	100	
U.A.E.[44]	D	79	
	A	18	

Table2: Distribution of HBV Genotypes in Some Iraqi Cities

Province	Genotype	%	Mean of %	Participants
Al-Anbar[45]	D	100	D= 96.8	80
Al Sulaymaniyah[37]	D	100	C= 1.6	33
Babylon[46]	C	8.5	B=0.74	60 (out of 141)
	A	5		
	B	4.3		
	D	2.1		
Baghdad[47]	D	95	A= 0.70	100
Duhok[48]	D	99		133
	B	1		
Mosul[49]	D	100		25
Samara[50]	D	93		87
	C	3.4		
Thi-Qar[36]	D	100	Total= 100%	24

Table 3: Mixed genotype infections in some Iraqi provinces

Province	Genotype	Percent	Frequency	Average	Participants
Baghdad[51]	BC, BD, BF, EF	37.5	3 genotypes= 13	35.1	80
	ABD, ABF, ACD, BCF, BDE & BEF	27.5			
	ABCF & BCDF	7.5			
	ABDEF & BCDEF	5.0			
Diwaniya[52]	A+B/C+D+ E	18.18	2 genotypes= 11	29.7	80
	B+C+D+E	15.15			
	C+D+E	12.12			
	A+B+C+D,D+E	6			
	B+D+E, A+C+D+E, A+D/E & E	3			
Diyala[53]	A+B+C+D	50	4 genotypes= 7	18.9	170
	D+E	14.3			
	A+B+D,B+C+D	7.1			
	B+D, C+D & E	7.1			
Wasit[54]	C+D	13	5 genotypes=4	10.8	100
	B+C	9			
	C+E	7			
	B+C+E	6	6 genotypes= 2	5.4 Total=~100%	
	A+B+C+D+F+ E/G	1			
	B / C	30/16			

Genotype A

Genotype 'A' of HBV is characterized by ubiquitous distribution across the continents as determined by whole genome sequencing. On the basis its epidemiological prevalence**,** HBV-A has been further phylogenetically subdivided into two subtypes HBV/Aa (Asian/African) and HBV/Ae (European), which are currently classified as sub-genotypes A1 and A2, respectively[5]. Additionally, HBV/A3 detected in Western Africa, along sub-genotypes A4, A5 and A7, have been assigned as novel quasi-sub-genotype A3 due to the lack of full genome sequencing data. More recently, sub-genotypes HBV/A6 and A8 showed limited regional distribution mainly in African countries[55]. Therapeutically, patients infected with either genotype A or B tend to have better response to interferon-based therapies compared to patients with other genotypes[56]. Genotype A is variably distributed in the Middle Eastern countries, ranging from 10% in both Saudi Arabia and Bahrain, to around 5% among Iraqi patients as detailed in Tables 1 and 2, respectively.

Genotype B

The HBV genotype B includes 10 sub-genotypes (B1-B10), and it has primarily prevalent in the Asian and the Arctic Circle region. While B1 exists in southern Japan; B2 was found to be a recombinant variant derived from genotypes B and C[57,58]. Although HBV/B is proposed to include 10 subgenotypes, this classification remains debated due to low nucleotide divergence (<4%), prompting some variants to be reclassified as quasi-sub-genotype B3[59]. In comparison with genotype C, HBV/B genotype has been less associated to induction of liver cirrhosis and HCC, but it has frequently observed in asymptomatic carriers and liver failure patients[60].As studied in Iraq, mixed genotype B and HBV/F infections comprised 72% of mixed genotype cases (Table 3).

Genotype C

Genotype C, comprised of seventeen sub-genotypes (C1-C17), is the mostly subdivided genotypes, with major distribution in the Pacific islands. More recently, the C17 sub-genotype was firstly recognized during 2020 in China[5]. This genotype has strongly believed to be associated with higher risk of liver cirrhosis and carcinoma[61], partly due to its potential of inducing breaks in the DNA and increasing the risk for chromosomal rearrangements via the accumulation of reactive species[62]. In Iraq, genotype C was found to be responsible for 8.5% of HBV cases in certain regions, while it accounted for 60% of infections in the Egyptian population (presented in Table 1).

Genotype D

HBV genotype D (D1-D12) has global existence, with predominantly prevalent in the regions of Mediterranean, India, and Russia. While D1-D4 showed a universal prevalence, D3 is particularly frequent in the European and the Mediterranean basin[63]. Remarkably, subtype D1 exhibits higher correlations with HCC risk and mutations as compared to other HBV/D sub-genotypes[64]. Also, genotype D demonstrated higher resistance to interferon-based therapies than other genotypes[65].

In Saudi Arabia, genotype D represents approximately 90% of all HBV cases. Its prevalence is even higher in Iraq, particularly in Thi-Qar and Al-Sulaymaniyah, where all recorded infections were caused by HBV/D. Similarly, it was the sole detected genotype in the Gaza Strip and Jordan, and the only reported genotype in Iranian studies. In Bahrain and Egypt, genotype D accounts for 61% and 40% of cases, respectively as presented in Tables 1 and 2.

Genotype E

Genotype E is predominantly limited to the Western and Central parts of the Africa, including sub-Saharan region. However, phylo-geographic analysis of HBV/E revealed minimum genetic diversity with a relatively recent reintroduction to the African population[66]. Interestingly, genotype E is characterized by the serosubytpe ayw4 as well as a unique initiation codon within the preS1 locus[67]**.** In Iraq, genotype E possesses a rare distribution, with a reported prevalence of 12% among patients. Likewise, in Saudi Arabia HBV/E accounted for 10% of detected genotypes (Tables 1 and 3).

Genotypes F and G

HBV/F is one of the most diffused and genetically diverse genotypes comprised of six sub-genotypes (F1-F6), with wide distribution and endemic nearly in all Central and South America. Clinically, sub-genotypes F1 and F2 are probably more associated to HCC than F3 or F4[67]. In Iraq, genotype F, detected in combination with genotype B, was found in approximately 70% of the mixed genotype infections as reported by Mohsen *et al* [51].

Genotype G, also termed the enigmatic HBV genotype because of its rarity and unclear biological features, exhibits the largest genome (~3248 nucleotides). Interestingly, HBV/G carries multiple mutations in both of the BCP and preC regions, as well as a distinctive insertion of 36 bp downstream of the core (c) initiation codon[68]. Genotype G was identified in only a single case in both Iraq and Turkey as reported by Hanash *et al*[54] and Sayan and Dogan [40].

Genotypes H, I and J

Genotypes H and F are characterized by the most genetic divergence, with up to 15% nucleotide variation compared to others. Though distributed globally, HBV/H is very rare outside America and it particularly higher among indigenous communities of Latin America [69, 70]. The HBV/H genotype has been noticed to have reduced expression of both HBeAg and DNA loads as well as to milder liver injury[71]. Its prevalence in Saudi Arabia was reported by Alshabi *et al*. to be 10% only [39].

HBV/I and J are the most recently recognized genotypes, and are predominantly originated in Asia.

The first identification of genotype I was from a Vietnamese case in 2008[72]. However, genotype I is subdivided into two subtypes with particular serosubtypes (adw2/ayw2), and considered an intermediate genotype, that resulted from recombination between genotypes A, C, and G[73,74].

Genotype J was firstly detected during 2009 from a Japanese patient with HCC in Borneo. Furthermore, this genotype exhibits the smallest genome of the HBV genotypes (except D), and a deletion of 33-bp in the preS1 region. Also, this genotype is considered a recombinant of HBV/C and Gibbon virus, possibly reflecting interspecies transmission[75,76]. To date, these three genotypes (H, I, and J) have not yet described as a part of circulating genotypes in the Middle East by any study.

CONCLUSION

Hepatitis B virus infections continue to constitute one of the highest causes of hepatocellular carcinoma, with persistent progressive spreading particularly across the developing countries. Despite the substantial success of global vaccination programs, the complete eradication of HBV infection remains unattainable goal in the foreseeable future. The molecular HBV genotype characterization HBV holds significant value in understanding regional distribution patterns, predicting therapeutic responses, and evaluating vaccine efficacy. Moreover, certain genotypes have demonstrated predominance both globally and regionally. While genotypes such as HBV/D, B, and F are widely widespread, other genotypes like H, I, and J appear to have more restricted geographical distributions. These variations may reflect underlying differences in ethnicity, socioeconomic conditions, climate, and the sensitivity or specificity as well was the purpose of genotyping techniques employed across different studies.

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