REVIEW ARTICLE

Molecular Epidemiology of Hepatitis B Virus in Pakistan: Link with Southern Asia

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ABSTRACT

Viruses and their genotypes reflect the relationship of their hosts. How these strains evolve, is one question and how they cross the borders is another. Since the HBV genotypes have been described by Okamoto and colleagues in 1988, Hepatitis B virus is expressed by a classification of different HBV strains into genetic genotypes and sub genotypes. A degree of 8% divergence between the groups has since then become the definition for HBV genotype. Now HBV is known by its geographic genotype and sub-genotype distribution. They also exhibit combination of both separately or in the form of a hybrid and hybrid of HBV genotypes is a common event in countries where movement of people is frequent across the borders, thus, providing a mixture of variation within individuals and in the population in general. It is seen that if travelling is by road then the different genotypes are prevalent around the borders, but if travelling is by air then they exist in general population as a less prevalent genotype. This review highlights the genotypic link between Pakistan and its South Asian neighbors.

KEY WORDS: *Hepatitis B Virus, Genetics, Genotypes.*

INTRODUCTION

Several scientific fields such as archaeology, anthropology and linguistics were used previously for the study of human migration. In the recent years, genetics has opened up new avenues and routes of human movement through study of mitochondria, viruses, Y chromosome and DNA sequence analysis.[11] Consequently, evaluation of nucleotide sequences showing their genotypes and sub-genotypes determine how much of their evolution can be reconstructed. HBV, especially changes form every time it crosses borders. These are ornamental changes which are part of the HBV armor associated with immunity and genome size, related to HBV genotypes.

Worldwide a strong correlation has been reported between HBV genotype and ethnicity since the genotypes have been described by Okamoto and colleagues in 1988.[2] HBV strains found worldwide differ having more than 8% genetic variability and eight HBV genotypes namely A, B, C, D, E, F, G, and H have been established on this basis.[3,4] Advances in phylogenetics has further resulted in recognition of subgenotypes of HBV genotypes based on more than 4% intra-genotypic divergence. Until now, the presence of 5 subgenotypes have been recognized for each of the HBV genotypes A, B, C and D, while 4 subgenotypes have been well reported for genotype F.[5-7]

In South East Asia the most prevalent genotype of hepatitis B virus is D. This review highlights the genotypic link between Pakistan and its South Asian neighbors. (Figure 1)

DISCUSSION

In Asia, initially, research on genotyping of HBV was conducted extensively in Japan and China, therefore, B and C the genotypes of these countries were considered as the most prevalent genotypes of Asia. Later on, it was found that all the seven HBV genotypes can be found in Asia[6], with predominance of D in South East Asia. Majority of South Asian countries where HBV genetics studies have been done genotype D has been found as predominant, whereas, the less prevalent genotype depends on the predominant genotype of the neighboring country. Thus HBV isolates sequences have shown that genotype D is predominant in India[8], Afghanistan[9], Iran.[10,11] Likewise, a similar pattern of genotype prevails in Pakistan with genotype D being the most prevalent.[12] Genotype D particularly happens to be the most widely distributed genotype and has been found scattered universally on the globe. However, the highest prevalence is in the belt stretching from Southern Europe and North Africa to India. Similarly Western and Southern Africa are of concern. Within the populations affected it has been noted that the intravenous drug users are the ones that fall prey to this genotype.[13-15]

HBV Genotypes of Pakistan

In Pakistan, multiple studies based on various population groups have been conducted to find out the prevalence of HBV infection.[16-18] All such studies present a varying rate of infection based on the study design, population selected, diagnostic assays and demographical and epidemiological variation. These study groups report HBV prevalence rate as 2–10% among healthy blood donors; 5–9% among health care personnel, 3.6–18.66% among the general population, 3.16% among the pregnant women, 10–20% in patients with provisional diagnosis of hepatitis and 3.16–10.4% among professional blood donors.[18]

HBV Genotypic Link with Neighbors

India:

Pakistan shares 2900 km of border with India. Population of Pakistan is ethnically and linguistically connected to India because of the several waves of migration from India to Pakistan. After partition in 1947 the immigrants settled in various parts of the country. Studies from India have generally reported predominance of genotype D coexisting with A and AD in lesser percentages. Hence a similar pattern is being seen in Pakistan. The appearance of genotype A has been linked to the migration from Europe over the time.[19] Since such migration was more prevalent in the Western and Northern states of Colonial India than in the Eastern region, this may well explain the rarity of genotype A in Eastern India as well as in Pakistani population. Further this has been

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confirmed by genetic studies from India involving mitochondrial DNA and Y chromosome.[20] Genotype C is also present in the populations of both countries. Genotype B has been reported from Pakistan but not from India although both B and C are the dominant genotypes reported in studies from South-East Asia and the Far East.[21, 22]

Bangladesh:

Bangladesh had been part of Pakistan from 1947 to 1971 and was known as East Pakistan. In Bangladesh, the predominant genotype is D (50%)[23] as that of rest of the subcontinent.[24] But Bangladesh also has C 37.5%, mixed C+D 7.5% and A and B each 2.5%.[25] Genotype A is present in a small percentage of population in the same way as in Pakistan and India. Since Bangladesh was also part of Indian subcontinent therefore, it exhibits the same pattern. The high prevalence of genotype C in the Bangladeshi population can be explained by their borders facing towards Far East and South-east Asia.[26] The Bangladeshis have had migratory links with the Mongolian ethnic group, hence a mixture of genotypes C and D is present. This is the only explanation available for the prevalence of genotype C is prevalent here, while elsewhere in the rest of Southeast Asia it is prevalence of D is more dominant. The reason for the presence of Genotype B in Bangladesh, as well as in Pakistan[27], is difficult to explain given that it has been designated as genotype characteristic of the Far East.[28]

Middle East:

HBV gene sequences analysis of these countries are consistent with Pakistan and show that HBV genotype D subtype *ayw2* is the most dominant.[29,30] Thousands of Pakistanis are residing in the Middle East for employment reasons. The majority of the countries which harbor Pakistani immigrants are UAE, Saudi Arabia, Qatar and Iran.

Iran:

Studies from Iran, another border sharing neighbor, show predominance of genotype D. Iran shares 912 km of border with Pakistan. Pilgrims in groups from Pakistan visit various holy places in Iran. Studies from Iran confirm that only genotype D exists in different regions of Iran.[31-33] Iran had also been a victim of influx of immigrants from neighboring countries which allows a potential introduction of other genotypes showing a mixed genotypic pattern in the general population. But phylogenetics in a recent study showed all isolates were clustering in a distinct branch of genotype D.[34] This probably can be explained on the basis that genotypic exposure was only limited to genotype D, whether they were refugees from Afghanistan or pilgrims from Pakistan.

Saudi Arabia:

Saudi Arabia has a very special place in Muslim world. Hundreds and thousands of Muslims visit holy places as pilgrims from all around the globe. Being a resource rich country thousands of migrants reside in Saudi Arabia for employment including Bangladeshis, Indians, and Pakistanis etc. From Pakistan every year millions visit the holy places as religious pilgrims. Majority of the pilgrims travel to the holy cities of Mecca and Medina, while the rest are scattered all over Saudi Arabia, especially in regions close to universities and medical colleges. If we look at Hepatitis B genotype in Saudis, it is a reflection of crowd that gathers. The Saudi study[35] on HBV shows that the majority of patients (64%) acquired HBV through unknown risk factors. Hepatitis B genotyping in patients revealed that major genotype is D (81.4%), whereas, other genotypes and their mixture are present in small percentages; A - 1.4%, C-1.4% and E- 5.7%. Also 10% had mixed genotype ADG, DE, DF and ADFG. This study needs to be further verified through bigger sample size.

Figure 1: graphic representation of genotypes distribution in Pakistan and neighboring countries.

Afghanistan:

Afghanistan shares 2640 km of border with Pakistan. The geographical terrain is difficult to maneuver around, much of this being quite mountainous, making crossing the border only practical through the numerous passes in the mountains. Yet border crossings are very common, which largely remain unchecked or uncontrolled. The prevalence of chronic HBV infection in Afghanistan was reported as 6.7% in 2003. The prevalence of HBsAg among Afghan refugees residing in camps in Balochistan, Pakistan was reported to be 8.3% in 2003 (WHO- UNICEF 2005). The predominant HBV genotype in Afghanistan was found to be genotype D having 95% bootstrap value on phylogenetics analysis.[36] Afghanistan is one place where people have been internally and externally displaced conferring higher chances of infected population of HBV and and other viruses. Prevalence of Genotype D of HBV shows that mixing of strains is within the population.

China:

The genotype distribution of HBV in china is most interesting. China lies in the north of Pakistan and India. China shares 510 km with Pakistan, and trade ventures between Pakistan and china are through the Khunjerab pass 16002 feet in the Karakoram Mountains connecting Pakistan's Gilgit–Baltistan Hunza - with the southwest border of the Xinjiang region of China The most common genotype of northern China is C, southern is B[37], whereas, in western China genotype D is found. Since China is an enormous country national travel is a normal phenomena and HBV recombinant viruses have been identified which are C/D recombinant hybrids.[38] Keeping in mind the geographical location of the China-Pakistan border, the area surrounding is related to the northern part of China, hence genotype C is prevalent in the adjoining part of Pakistan.[39]

CONCLUSION

Researchers in general agree that the prevalence of HBV genotypes throughout the world is clearly linked to trade and migration. Hepatitis B genotype D is the most prevalent genotype worldwide but its epidemiological tracking history is still not very clear. Zehender et al[40] has done Phylogeographical analysis of HBV genotype D by reconstructing the epidemiological history of HBV-D genotype through phylodynamically and phylogeographical studies. Their study shows that Indian sub-continent had the highest posterior probability to be the location of the tree root of genotype D which suggests that the India was the place in which HBV-D originated. As a result of frequent exchanges with neighbors this genotype penetrated into neighboring areas.

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