A Global Perspective on Hepatitis B-Related Single Nucleotide Polymorphisms and Evolution During Human Migration

Dar-In Tai, Wen-Juei Jeng, and Chun-Yen Lin

Genome-wide association studies have indicated that human leukocyte antigen (HLA)-DP and HLA-DQ play roles in persistent hepatitis B virus (HBV) infection in Asia. To understand the evolution of HBV-related single nucleotide polymorphisms (SNPs) and to correlate these SNPs with chronic HBV infection among different populations, we conducted a global perspective study on hepatitis-related SNPs. We selected 12 HBV-related SNPs on the HLA locus and two HBV and three hepatitis C virus immune-related SNPs for analysis. Five nasopharyngeal carcinoma-related SNPs served as controls. All SNP data worldwide from 26 populations were downloaded from 1,000 genomes. We found a dramatic difference in the allele frequency in most of the HBV- and HLA-related SNPs in East Asia compared to the other continents. A sharp change in allele frequency in 8 of 12 SNPs was found between Bengali populations in Bangladesh and Chinese Dai populations in Xishuangbanna, China ($P < 0.001$); these areas represent the junction of South and East Asia. For the immune-related SNPs, significant changes were found after leaving Africa. Most of these genes shifted from higher expression genotypes in Africa to lower expression genotypes in either Europe or South Asia ($P < 0.001$). During this two-stage adaptation, immunity adjusted toward a weak immune response, which could have been a survival strategy during human migration to East Asia. The prevalence of chronic HBV infection in Africa is as high as in Asia; however, the HBV-related SNP genotypes are not present in Africa, and so the genetic mechanism of chronic HBV infection in Africa needs further exploration. *Conclusion:* Two stages of genetic changes toward a weak immune response occurred when humans migrated out of Africa. These changes could be a survival strategy for avoiding cytokine storms and surviving in new environments. (*Hepatology Communications* 2017;1:1005-1013)

Introduction

Chronic hepatitis B virus (HBV) is a global disease. The majority of carriers of hepatitis B surface antigen (HBsAg) are inhabitants of Africa and Asia.[1,2] Immune tolerance is a hallmark of persistent HBV infection.[3] Typically, patients with chronic hepatitis B are infected through their parents in the early stage of life.[4] Remarkably, the immune system of the host may respond to the HBV[5] but does not produce the immune clearance of HBV. HBV may replicate in host cells peacefully until they enter immune clearance phases 2-4 decades later.[3] If the HBV can be eradicated, HBV replication will be terminated, and ultimately 50% of hosts may clear HBsAg by 80 years of age.[6] Genome-wide association studies from Asia have revealed that the human leukocyte antigen (HLA)-DP and HLA-DQ loci play roles in persistent HBV infection. [7-13] Our objective is to understand the evolution of the single nucleotide

Abbreviations: BEB, Bengali in Bangladesh; CD40, clusters of differentiation molecule 40; CDX, Chinese Dai in Xishuangbanna, China; CFB, complement factor B; GIH, Gujarati in India; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HLA, human leukocyte antigen; IFNL4, interferon lambda 4; LWK, Luhya in Webuye, Kenya; NPC, nasopharyngeal carcinoma; SNP, single nucleotide polymorphism.

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polymorphisms (SNPs) that were responsible for HBV-related immune tolerance during human migration and to correlate the HBV-related SNPs with a prevalence of chronic HBV infection among global populations. Based on the data from 1,000 genomes collected worldwide, we conducted a global perspective study on the allele frequency of hepatitis-related SNPs.

Materials and Methods

Based on a literature review, 12 HBV- and HLA-related SNPs,[7-13] five hepatitis- and immune-related SNPs in complement factor B (CFB), clusters of differentiation molecule 40 (CD40), and interferon lambda 4 (IFNL4) loci[14-18], and five nasopharyngeal carcinoma (NPC)-related SNPs in HLA regions[19-21] were selected for this analysis (Tables 1 and 2). These SNP data from around the world were downloaded from the phase 3 data of 1,000 genomes (http://www.1000genomes.org/).[22] The subjects participating in the 1,000 genome project were older than 18 years and had three out of four grandparents who identified themselves as members of the group. The location of the 26 populations evaluated in the 1,000 genomes are shown by abbreviation on a global HBsAg prevalence map reported by Hou et al.[2] (Fig. 1). The allele frequencies of different geographic groups in viral hepatitis-related SNPs and NPC-related SNPs are illustrated in Fig. 2. The SNP genotype differences between groups are listed in Tables 1 and 2. We used interactive chi-square tests to calculate the difference in genotypes between groups (http://quantpsy.org).

Results

Among two HBV- and immune-related SNPs in the CFB and CD40 regions[14,15] and three hepatitis C virus-related SNPs in the IFNL4 regions,[16-18] allele type differences can be found between Africa and Europe or between Africa and South Asia (Fig. 2A). All these immune-related SNP genotypes differed significantly between Esan in Nigeria and Toscani in Italy and between Luhya in Webuye, Kenya (LWK) and Gujarati in India (GIH) (Table 1; $P < 0.001$).

Among 12 HBV- and HLA-related SNPs,[7-13] the allele frequency showed marked differences between South and East Asian genome samples (Fig. 2B). Eight of the 12 SNPs differed significantly between Bengali in Bangladesh (BEB) and Chinese Dai in Xishuangbanna, China (CDX); these areas represent the junction of South and East Asia (Table 2; $P < 0.001$).

Three of the 12 HBV- and HLA-related SNPs (Fig. 2B, dotted lines; rs9276370, rs3128917, and rs9380343) also showed significant differences between LWK in Africa and GIH in South Asia (Table 2; $P < 0.001$). In contrast, we found the allele frequency of NPC-related SNPs[18-20] to be relatively stable among different populations (Fig. 2C).

Discussion

Based on the well-known human migration pathways[23,24] and the recent data from 1,000 genomes,[22] our analysis of hepatitis- and immune-related SNPs demonstrate a significant change in allele frequency shortly after the migration out of Africa (Fig. 2A). All genotypes of five immune-related SNPs differed significantly between Esan in Nigeria in Africa and Toscani in Italy in Europe and between LWK in Africa and GIH in South Asia (Table 1; $P < 0.001$). In addition, both CFB and CD40 shifted from a higher expression in African genotypes (rs12614:TT; rs1883832:CC) to a lower expression in European and South Asian genotypes (rs12614:CC; rs1883832:TT).[14,15] These changes conferred a decrease in the strength of immune responses. The CC genotype of

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TABLE 1. GENOTYPE DIFFERENCES BETWEEN GEOGRAPHIC AREAS ON HEPATITIS- AND IMMUNE-RELATED SNPS

		TSI (n = 107)		ESN (n = 99)		TSI Vs. ESN	LWK (n = 103)		GIH (n = 99)		LWK Vs. GIH	BEB (n = 86)		CDX (n = 93)		BEB Vs. CDX
SNP	Genotype	No	%	No	%	*P* value	No	%	No	%	*P* value	No	%	No	%	*P* value
rs12614	CC	76	71.0	37	37.4		45	45.5	74	71.9		68	79.1	90	96.8	
CFB	CT	29	27.1	47	47.5		45	45.5	25	24.3		17	19.8	3	3.2	
	TT	2	1.9	15	15.1	1.1×10^{-6}	9	9.0	4	3.9	6.25×10^{-6}	1	1.2	0	0	1.1×10^{-3}
rs12979860	CC	37	34.6	8	8.1		18	18.2	62	60.2		53	61.6	75	80.6	
IFNL4	CT	55	51.4	41	41.4		60	60.6	33	32.0		32	37.2	17	18.3	
	TT	15	14.0	50	50.5	0.0000	21	21.2	8	7.8	6.6×10^{-4}	1	1.2	1	1.1	1.7×10^{-2}
rs368234815	--	15	14.0	52	52.5		25	25.3	8	7.8		1	1.2	1	1.1	
IFNL4	-T	56	52.3	38	38.4		60	60.6	33	32.0		33	38.4	17	18.3	
	TT	36	33.7	9	9.1	0.0000	14	14.1	62	60.2	0.0000	52	60.5	75	80.6	1.1×10^{-2}
rs8099917	TT	64	59.8	95	96.0		84	84.8	72	69.9		67	77.9	75	80.6	
IFNL4	GT	42	39.3	4	4.0		15	15.2	29	28.2		19	22.1	18	19.4	
MSRB1P1																
	GG	1	0.9	0	0	1×10^{-8}	0	0	2	1.9	2.6×10^{-2}	0	0	0.0	0.0	1.0000
rs1883832	TT	2	1.9	0	0		0	0	6	5.8		9	10.5	29	31.2	
CD40	CT	60	56.1	0	0		8	8.1	46	44.7		36	41.9	44	47.3	
	CC	45	42.1	99	100	0.0000	91	91.9	51	49.5	0.0000	41	47.7	20	21.5	1.7×10^{-2}

Abbreviations: BEB, Bengali populations from Bangladesh; CDX, Chinese Dai populations in Xishuangbanna, China; ESN, Esan in Nigeria; GIH, Gujarati in India from Houston, TX; LWK, Luhya in Webuye, Kenya; MSRB1P1, methionine sulfoxide reductase B1 pseudogene 1; TSI, Toscani in Italy.

TABLE 2. GENOTYPE DIFFERENCES BETWEEN GEOGRAPHIC AREAS ON HBV- AND HLA-RELATED SNPS

		TSI (n = 107)		ESN (n = 99)		TSI Vs. ESN	LWK (n = 103)		GIH (n = 99)		LWK Vs. GIH	BEB (n = 86)		CDX (n = 93)		BEB Vs. CDX
SNP	Genotype	No	%	No	%	*P* value	No	%	No	%	*P* value	No	%	No	%	*P* value
rs9276370	GG	16	15.0	53	53.5		41	41.4	6	5.8		0	0.0	0	0.0	
HLA-DQA2	GT	42	39.3	41	41.4		43	43.4	34	33.0		22	25.6	18	19.4	
	TT	49	45.8	5	5.1	0.0000	15	15.2	63	61.2	0.0000	64	74.4	75	80.6	0.6071
rs7756516	CC	13	12.1	41	41.4		29	29.3	13	12.6		2	2.3	0	0.0	
HLA-DQB2	CT	54	50.5	49	49.5		47	47.5	47	45.6		35	40.7	20	21.5	
	TT	40	37.4	9	9.1	4.0×10^{-8}	23	23.2	43	41.7	2.3×10^{-3}	49	57.0	73	78.5	5.1×10^{-3}
rs7453920	AA	12	11.2	8	8.1		7	7.1	6	5.8		0	0.0	0	0.0	
HLA-DQB2	AG	41	38.3	48	48.5		42	42.4	29	28.2		19	22.1	11	11.8	
	GG	54	50.5	43	43.4	0.3181	50	50.5	68	66.0	0.0771	67	77.9	82	88.2	0.1850
rs9277341	TT	44	41.1	6	6.1		18	18.2	21	20.4		14	16.3	1	1.1	
HLA-DPA1	CT	47	43.9	41	41.4		43	43.4	57	55.3		42	48.8	23	24.7	
	CC	16	15.0	52	52.5	0.0000	38	38.4	25	24.3	0.0909	30	34.9	69	74.2	1.1×10^{-7}
rs3135021	GG	55	51.4	45	45.5		33	33.3	26	25.2		29	33.7	65	69.9	
HLA-DPA1/B1	AG	40	37.4	43	43.4		46	46.5	63	61.2		45	52.3	27	29.0	
	AA	12	11.2	11	11.1	0.6561	20	20.2	14	13.6	0.1074	12	14.0	1	1.1	1.1×10^{-6}
rs9277535	AA	51	47.7	61	61.6		62	62.6	52	50.5		40	46.5	13	14.0	
HLA-DPB1	AG	50	46.7	34	34.3		32	32.3	48	46.6		30	34.9	42	45.2	
	GG	6	5.6	4	4.0	0.1329	5	5.1	3	2.9	0.0949	16	18.6	38	40.9	4.8×10^{-6}
rs10484569	GG	100	93.5	83	83.8		88	88.9	95	92.2		82	95.3	33	35.5	
HLA-DPA2	AG	7	6.5	15	15.2		10	10.1	8	7.8		3	3.5	41	44.1	
	AA	0	0.0	1	1.0	0.0748	1	1.0	0	0.0	0.4939	1	1.2	19	20.4	0.0000
rs3128917	TT	54	50.5	25	25.3		28	28.3	59	57.3		44	51.2	22	23.7	
HLA-DPA2	GT	44	41.1	48	48.5		51	51.5	39	37.9		32	37.2	42	45.2	
	GG	9	8.4	26	26.3	8.3×10^{-5}	20	20.2	5	4.9	2.1×10^{-5}	10	11.6	29	31.2	1.4×10^{-4}
rs2281388	GG	103	96.3	99	100.0		99	100	96	93.2		81	94.2	33	35.5	
HLA-DPA2	AG	4	3.7	0	0.0		0	0.0	7	6.8		4	4.7	41	44.1	
	GG	0	0.0	0	0.0	0.1516	0	0.0	0	0.0	0.0307	1	1.2	19	20.4	0.0000
rs3117222	CC	54	50.5	25	25.3		28	28.3	59	57.3		44	51.2	21	22.6	
HLA-DPA2	CT	44	41.1	50	50.5		51	51.5	39	37.9		32	37.2	43	46.2	
	TT	9	8.4	24	24.2	1.5×10^{-4}	20	20.2	5	4.9	2.1×10^{-5}	10	11.6	29	31.2	8.4×10^{-5}
rs9380343	CC	99	92.5	93	93.9		95	96.0	95	92.2		82	95.3	31	33.3	
HLA-DPB2	CT	8	7.5	6	6.1		4	4.0	8	7.8		3	3.5	43	46.2	
	TT	0	0.0	0	0.0	0.9217	0	0.0	0	0.0	0.5339	1	1.2	19	20.4	0.0000
rs9366816	TT	65	60.7	65	65.7		64	64.6	65	63.1		58	67.4	24	25.8	
HLA-DPA3	CT	37	34.6	29	29.3		32	32.3	35	34.0		25	29.1	47	50.5	
	CC	5	4.7	5	5.1	0.7189	3	3.0	3	2.9	0.9690	3	3.5	22	23.7	2.0×10^{-8}

Abbreviations: BEB, Bengali populations from Bangladesh; CDX, Chinese Dai populations in Xishuangbanna, China; ESN, Esan in Nigeria; GIH, Gujarati in India from Houston, TX; LWK, Luhya in Webuye, Kenya; MSRB1P1, methionine sulfoxide reductase B1 pseudogene 1; TSI, Toscani in Italy.

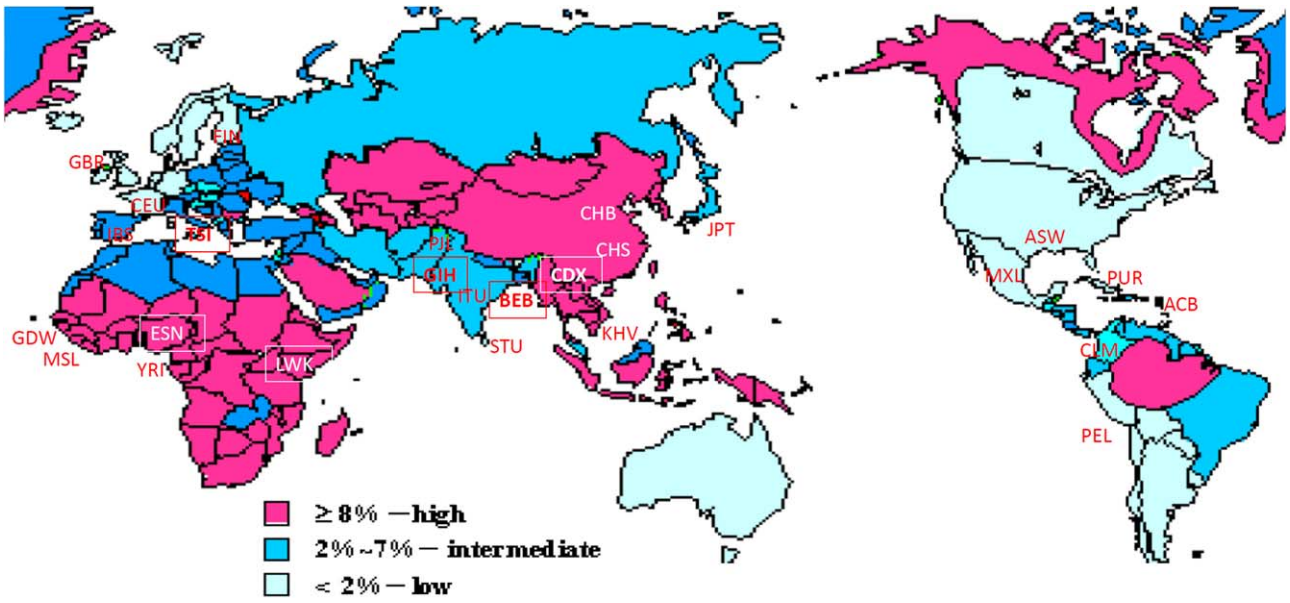

FIG. 1. Global HBsAg prevalence before HBV vaccination and the locations of the population groups of 1,000 genomes. The boxed groups are populations used in Tables 1 and 2. (Modified from Hou et al., Int J Med Sci 2005; 2:50-57.) Abbreviations: ACB, African Ancestry from Barbados in the Caribbean; ASW, African ancestry in Southwest United States; BEB, Bengali in Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah residents with ancestry from Northern and Western Europe; CHB, Han Chinese in Beijing, China; CHS, Han Chinese South, China; CLM, Colombians in Medellin, Colombia; ESN, Esan from Nigeria; FIN, Finnish in Finland; GBR, British from England and Scotland, United Kingdom; GDW, Gambian in Western division, Gambia, GIH, Gujarati Indians in Houston, TX; IBS, Iberian populations in Spain; ITU, Indian Telugu in the United Kingdom; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Hochi Minh city, Vietnam; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; MXL, Mexican ancestry in Los Angeles, CA; PEL, Peruvian in Lima, Peru; PJL, Punjabi in Lahore, Pakistan; PUR, Puerto Ricans in Puerto Rico; STU, Sri Lankan Tamil in the United Kingdom; TSI, Toscani in Italy; YRI, Yoruba in Ibadan, Nigeria.

rs12979860 (IFNL4), which is more prevalent in East Asia, is associated with a lower baseline IFNL3 (interleukin-28B) expression.[16,17] The IFNL4 open reading frame is truncated by a polymorphic frame-shift insertion (rs368234815), which turns IFNL4 into a polymorphic pseudogene in East Asian populations.[18] Because the prevalence of HBsAg is higher in Africa than in Europe or South Asia, these trends of decreased immune protein expression are not related to HBV-specific immune tolerance. Although it is clear that Europeans and South Asians are two different races, they showed similar genetic adaptions when they migrated out of Africa. These changes suggest that the decreased expression of immune-related genes might have been an important survival strategy when humans migrated into new territories and faced new pathogens. The contact between different races of humans may induce devastating diseases, for example, when the New World was discovered by Christopher Columbus in 1492.[25] A similar situation was well documented when Japan sent troops to Taiwan in 1874 and 1895; only 0.1% to 0.3% of soldiers died in battle, while around 10% died of diseases in a short period of time after arrival.[26]

Our second principal result is that the allele frequency of HBV- and HLA-related SNPs show marked differences between South and East Asian genome samples (Fig. 2B). Eight of the 12 SNPs differed significantly between BEB and CDX (Table 2; $P < 0.001$). These two populations are located at the junction of South and East Asia. The unique allele types of HBV-related SNPs in East Asian populations are different from those of other geographic populations. These genotypic changes could be related to antigen presentation and could be associated with persistent HBV infection.[7-13] Our findings are in agreement with a higher prevalence of HBsAg in East Asia than in South Asia (Fig. 1). These genotypic populations are generally overlapped in the Y chromosome haplogroup O1-O3 distribution map (https://en.wikipedia.org/wiki/Human_Y-chromosome_DNA_haplogroup) as they started in the Indo-China Peninsula and travelled to northern China and Japan.

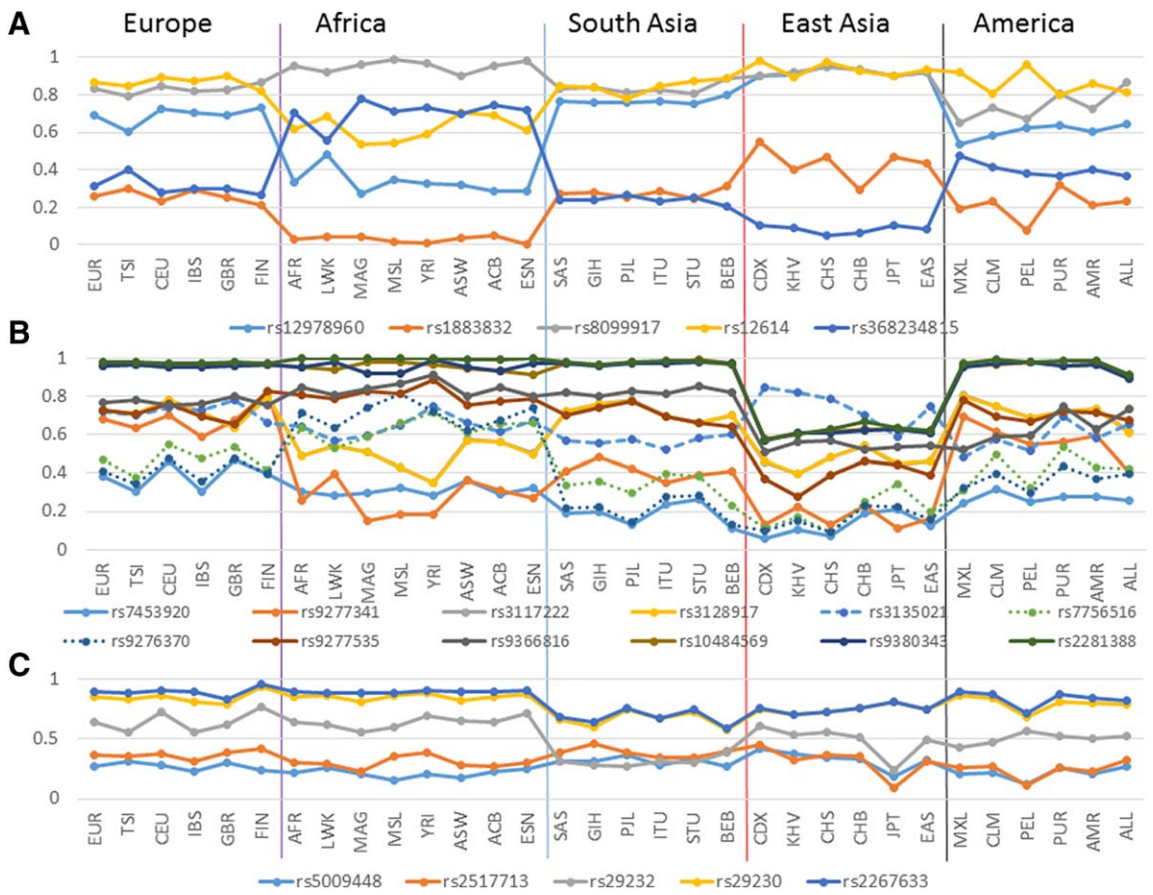

FIG. 2. Allele frequency of viral hepatitis- and NPC-related SNPs in different geographic groups. (A) Allele frequency of immune-related SNPs (CFB, CD40, IFNL4). Significant allele type differences were found between African and European populations and between African and South Asian populations in all of the immune-related SNPs. (B) Allele frequency of HBV- and HLA-related SNPs (HLA-DP and -DQ). Significant allele type differences were found between South and East Asian populations in 8 of 12 HLA-related SNPs and between African and South Asian populations in 3 of 12 SNPs. (C) Allele frequency of NPC-related SNPs (HLA regions). There was no significant difference among different populations in five NPC-related SNPs. Abbreviations: ACB, African Ancestry from Barbados in the Caribbean; AFR, Africa, total; ALL, global, total; AMR, America, total; ASW, African ancestry in Southwest United States; BEB, Bengali in Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah residents with ancestry from Northern and Western Europe; CHB, Han Chinese in Beijing, China; CHS, Han Chinese South, China; CLM, Colombians in Medellin, Colombia; EAS, East Asia, total; ESN, Esan from Nigeria; EUR, Europe, total; FIN, Finnish in Finland; GBR, British from England and Scotland, United Kingdom; GIH, Gujarati Indians in Houston, TX; IBS, Iberian populations in Spain; ITU, Indian Telugu in the United Kingdom; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Hochi Minh city, Vietnam; LWK, Luhya in Webuye, Kenya; MAG, Mandinka in Gambia; MSL, Mende in Sierra Leone; MXL, Mexican ancestry in Los Angeles, CA; PEL, Peruvian in Lima, Peru; PJL, Punjabi in Lahore, Pakistan; PUR, Puerto Ricans in Puerto Rico; SAS, South Asia, total; STU, Sri Lankan Tamil in the United Kingdom; TSI, Toscani in Italy; YRI, Yoruba in Ibadan, Nigeria.

Given the results, we theorized on the reason behind the dramatic allele differences in HBV-related SNPs between BEB in South Asia and CDX in East Asia. One possible explanation for this variation involves the consideration of environmental landscape factors.[27] For example, Bangladesh is a predominately rich, fertile, and flat land, with many areas situated less than 12 m above sea level. On the other hand, Xishuangbanna is situated in a mountainous and forested area that has the largest diversity of plants and animals in China.

Regions with higher plant and animal biodiversity are often accompanied by an increased range and abundance of vector-borne or nonvector-borne diseases.[28-34] Accordingly, the inhabitants of these areas should be able to tolerate an increased number of unfamiliar microorganisms. We speculated that the subjects who demonstrate direct and strong immune responses

TABLE 3. DIFFERENCES IN CHRONIC HBV INFECTION BETWEEN AFRICA AND EAST ASIA

	Africa	East Asia
HBsAg prevalence	High	High
Host gene pattern		
HBV- and HLA- related SNPs	Rare	Common
Immune-related SNPs	High expression	Low expression
HBV genotype	A,D,E	B,C
Vertical transmission	Low	High
Early HBeAg seroconversion	Common	Low

may die of a cytokine storm in fulminant hepatitis, severe acute respiratory syndrome, influenza, and other infections.[30-34] This concept is supported by a lower mortality rate from influenza H1N1 in Asia than in Australia, New Zealand, and North America.[35]

Cytokine storm was first described in graft-versus-host disease and was soon also identified in many infectious diseases[36]; many cytokines, chemokines, and complements are involved.[37-39] The immune-related SNPs selected in this study that included IFN (IFNL4), tumor necrosis factor-receptor (CD40), and complements (CFB) are all participants in cytokine storms. HLA class II molecules are associated with antigen presentation and are also modulated by cytokines.[40] A cytokine storm is considered to be a hyper-reaction of the immune response to a pathogen that may cause fulminant disease and mortality.[36-39] When humans migrate to a new territory, they face many unfamiliar pathogens. Those subjects with a strong immune response will die of disease, but those subjects with a weak immune response to the pathogens may survive. Chronic HBV infection with an immune tolerance stage is an example of a weak immune response.[3-5]

East Asian populations carry similar allele types of HBV-related SNPs (Fig. 2B), although the environments of northern China and Japan differ substantially from those of southern China and the Indo-China Peninsula.[41] We therefore propose that there was a significant physical block to gene flow on the Indo-China Peninsula. Most of the survivors in East Asia exhibit delayed HBV-related immune clearance genotypes. This could have been a survival strategy to pass through the Indo-China Peninsula and southern China during human migration. Such HLA class II genotypes are aimed toward an immune tolerance strategy.[7-13] These changes were successful because this group of people spread to northern China and Japan and have become the largest population in the world numerically. However, such a survival benefit may have been a trade-off with cold tolerance as these populations were unable to cross the Bering Strait in large numbers. Indigenous Americans do not show the same HBV-related allele pattern; they have a low prevalence of chronic HBV infection and high influenza-related mortality rates.[1,2,35]

Overall, we identified two genetic adaptations that occurred during human migration. The first was the decreased expression of immune-related genes after leaving Africa; the second was the evolution of an HLA system with migration into the Indo-China Peninsula. Both events may have aimed to decrease the strength of the immune response and avoid cytokine storms when facing different types of pathogens. The high prevalence of chronic HBV infection in East Asia could be a consequence of such a strategy. However, persistent HBV infection-related HLA genotypes are not present in the African population (Fig. 2B) and cannot be responsible for the high prevalence of HBsAg in Africa.

Different genetic and nongenetic mechanisms of chronic HBV infection are presented between East Asian and African populations.[4,42-44] We summarize the differences on HBsAg carriers between East Asia and Africa in Table 3. These differences may provide a clue for the mechanism of the function of SNPs in the persistent HBV infection. The high prevalence of low-expression-type immune-related SNPs and chronic HBV infection-related SNPs on the HLA locus may be a reason for a longer hepatitis B e antigen (HBeAg)-positive phase in East Asia. IFN-alpha has been recommended for treatment of HBeAg-positive chronic hepatitis B. In a larger series from pediatric patients, IFN-alpha was found to be an effective therapy in chronic hepatitis B with severe inflammation that facilitates HBeAg seroconversion in earlier life.[45] In addition, HBV- and HLA-related SNPs are also associated with spontaneous HBeAg seroconversion.[46-48] These genetic polymorphisms could be a reason for an early HBeAg seroconversion and a lower vertical transmission in Africa compared to East Asia.

It is well known that HBV genotypes A, B, and D show an earlier HBeAg seroconversion compared to genotype C.[42,44] This early HBeAg seroconversion was suggested to be the reason of low vertical transmission in Africa.[49] However, HBV genotype B also had an early HBeAg seroconversion but had a high vertical transmission rate in East Asia.[4] Therefore, host factors rather than HBV genotypes alone should be considered for the high vertical transmission rate in East Asia. Most HBV-related genome-wide association

studies were done in East Asia. We need studies to understand the genetic roles in persistent HBV infection in African populations.

Our study found two stages of genetic changes toward a weak immune response when humans migrated out of Africa. These changes could be a survival strategy for avoiding cytokine storms and surviving in new environments.

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