

**Evolution of full-length genomes of HBV quasispecies in sera of patients with a
coexistence of HBsAg and anti-HBs antibodies**

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Figure S1 Phylogenetic tree reconstructed for filtered sequences, which excluded sequences containing premature termination codons. This tree was used to calculate selective pressure. Phylogenetic trees were reconstructed from the concatenated four protein-coding nucleotide alignments excluding sequences with stop codon mutations, deletion and insertion frameshifts.

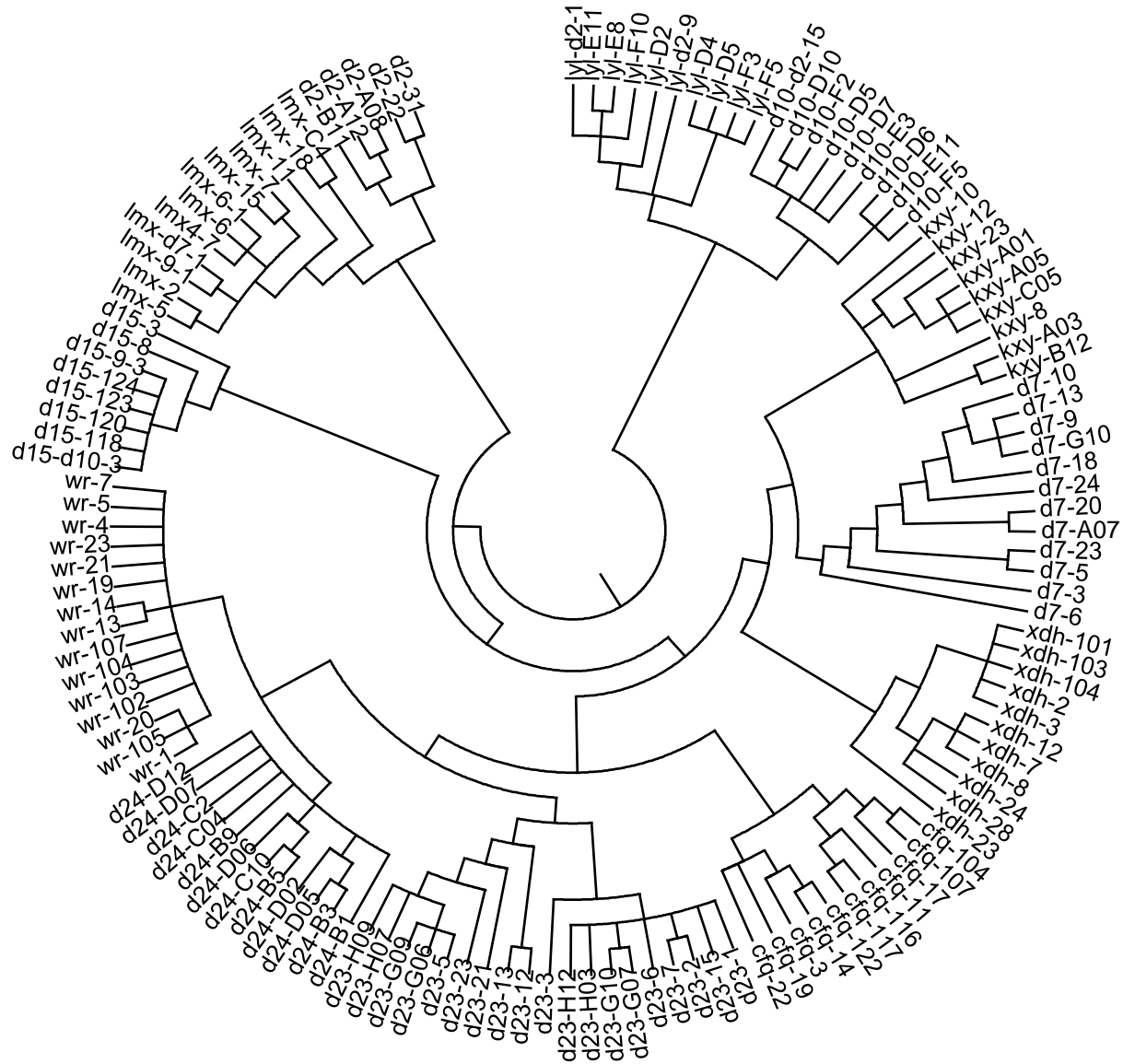


Table S1 Quasispecies complexity (Sn) of each nucleotide position (nt1 to 3215) between the patients with coexisting HBsAg and anti-HBs and controls.

Region of variation (level)	Experimental group(mean± SE)(n=6)	Control group (mean ±SE)(n=6)	P value*
Genotype C			
Full length (nt)	0.0362±0.0012	0.0318±0.0013	0.001
Large HBsAg (nt)	0.0496±0.0027	0.021±0.0021	<0.001
Middle HBsAg (nt)	0.0343±0.003	0.0163±0.0022	<0.001
HBsAg (nt)	0.0305±0.0033	0.0137±0.0023	<0.001
HBxAg (nt)	0.0333±0.0023	0.0251±0.0025	0.002
Procore/core(nt)	0.027±0.0017	0.031±0.002	0.058
Polymerase (nt)	0.0474±0.0019	0.0259±0.0017	<0.001
RT region (nt)	0.0365±0.0011	0.0303±0.0011	0.001
Genotype B/C/I			
Full length (nt)	0.0484±0.0012	0.0387±0.0013	<0.001
Large HBsAg (nt)	0.0593±0.001	0.0406±0.0009	<0.001
Middle HBsAg (nt)	0.0588±0.0009	0.0403±0.0008	<0.001
HBsAg (nt)	0.0581±0.0009	0.0398±0.0008	<0.001
HBxAg (nt)	0.0578±0.0008	0.0401±0.0008	<0.001
Procore/core(nt)	0.0566±0.0009	0.0412±0.0008	<0.001
Polymerase (nt)	0.0551±0.001	0.0405±0.001	<0.001
RT region (nt)	0.0566±0.0008	0.0413±0.0008	<0.001

*Paired-samples T test

Table S2 Epitopes for HBxAg, LHBsAg, PreC/C and Polymerase.

Epitope ID	Linear sequence	nt Starting Position	nt Ending Position	Antigen Name	Epitope types
34101	VGAESCGRPFSGSLG	1434	1478	HBxAg	HLAI T cell epitopes
37187	KVLHKRTLGLSAMST	1644	1688	HBxAg	HLAI T cell epitopes
36354	CAFSSAGPCALRFTS	1554	1598	HBxAg	HLAII T cell epitopes
31898	QLDPARDVL	1395	1421	HBxAg	HLAI T cell epitopes
34027	VLCLRPVGA	1416	1442	HBxAg	HLAI T cell epitopes
36402	LRFTSARRMETTVN	1584	1625	HBxAg	HLAI T cell epitopes
37181	TTVNAHOILPKVLHK	1614	1658	HBxAg	HLAI T cell epitopes
37466	KVLHKRTLGL	1644	1673	HBxAg	HLAI T cell epitopes
37919	VLHKRTLGL	1647	1673	HBxAg	HLAI T cell epitopes
38701	SAMSTTDLEAYFKDC	1674	1718	HBxAg	HLAI T cell epitopes
40624	EIRLMIFVLGGCRHK	1749	1793	HBxAg	HLAI T cell epitopes
40664	ETRLMIFVLGGCRHK	1749	1793	HBxAg	HLAI T cell epitopes
28447	MAARLCCQLDPARDV	1374	1418	HBxAg	HLAII T cell epitopes
34102	SGSLGTLSSPSPSAV	1464	1508	HBxAg	HLAII T cell epitopes
37786	KVLHKRTLGLSAMSTT	1644	1691	HBxAg	HLAII T cell epitopes
37943	GLSAMSTTDL	1668	1697	HBxAg	HLAII T cell epitopes
39347	YFKDCLFKDWEELGEE	1704	1751	HBxAg	HLAII T cell epitopes
39706	CLFKDWEEL	1716	1742	HBxAg	HLAII T cell epitopes
41238	VFVLGGCRHKLVCAAPC	1764	1823	HBxAg	HLAII T cell epitopes
42384	VLGGCRHKL	1770	1796	HBxAg	HLAII T cell epitopes
42443	KLVCSAPC	1791	1817	HBxAg	HLAII T cell epitopes
35398	HLSLRGLFV	1527	1553	HBxAg	B cell epitopes
39089	YFKDCLFKDWEELGE	1704	1748	HBxAg	B cell epitopes
40283	EELGEEIRLKVFLG	1734	1778	HBxAg	B cell epitopes
41004	VFVLGGCRHKLVCAAPC	1764	1808	HBxAg	B cell epitopes
41238	VFVLGGCRHKLVCAAPC	1764	1823	HBxAg	B cell epitopes
42443	KLVCSAPC	1791	1817	HBxAg	B cell epitopes
44684	LVCAPAPCNFF TSA	1794	1835	HBxAg	B cell epitopes
34103	SPSAVPTDHGAHLSL	1494	1538	HBxAg	B cell epitopes
2758	FLGPLLVLOA	143	172	LHBsAg	HLAI T cell epitopes
6556	FLLTRILTI	176	205	LHBsAg	HLAI T cell epitopes
6631	FLLTRILTI	179	205	LHBsAg	HLAI T cell epitopes
16755	STGPCKTCTT	503	532	LHBsAg	HLAI T cell epitopes
16795	SMYPSCCCTK	515	544	LHBsAg	HLAI T cell epitopes
16796	CTTPAQGNSMFPSC	524	565	LHBsAg	HLAI T cell epitopes
16836	MFPSCCCT	551	574	LHBsAg	HLAI T cell epitopes
16857	IPIPSSWAF	569	595	LHBsAg	HLAI T cell epitopes
21139	LWEWASVRF	605	631	LHBsAg	HLAI T cell epitopes
21145	SWLSLLVPF	632	658	LHBsAg	HLAI T cell epitopes
21146	YLWEWASVR	635	661	LHBsAg	HLAI T cell epitopes
23151	GLSPTVWLSV	674	703	LHBsAg	HLAI T cell epitopes
24299	PFMPLPIFF	752	781	LHBsAg	HLAI T cell epitopes
423053	TNLSVNPPLGFFPDHOLDP	2887	2943	LHBsAg	HLAI T cell epitopes
423063	PLGFFPDHQLDPAFGANSN NPDWDFNP	2908	2988	LHBsAg	HLAI T cell epitopes
462003	PTPFSPLRD	3160	3189	LHBsAg	HLAI T cell epitopes
462107	MQWNSTTFHQTLQDPRVR GLYFPAGG	3172	34	LHBsAg	HLAI T cell epitopes
462159	NSTTFHQTLQDPRVRGLYF PAGGSSSGTVNPVPTTVSPI SSIFSRIGD	3181	109	LHBsAg	HLAI T cell epitopes
5911	VLQAGFFLL	161	187	LHBsAg	HLAII T cell epitopes
5976	AGFFLLTRILTI PQS	170	214	LHBsAg	HLAII T cell epitopes
7328	GGTPACPG	281	304	LHBsAg	HLAII T cell epitopes
11748	GYRWMCLRR	365	391	LHBsAg	HLAII T cell epitopes
11997	ILLLCLIFL	377	403	LHBsAg	HLAII T cell epitopes
12566	ILLLCLIFLL	377	406	LHBsAg	HLAII T cell epitopes
15063	LLDYQGMLPV	410	439	LHBsAg	HLAII T cell epitopes
22023	LLVPFVQWFV	644	673	LHBsAg	HLAII T cell epitopes
22025	LVPFVQWFVGLSPTV	647	691	LHBsAg	HLAII T cell epitopes
23991	SVIWMMWYW	698	724	LHBsAg	HLAII T cell epitopes

1799	SSGTVSPAQNTVSAISSI	71	124	LHBsAg	B cell epitopes
6632	FLLTKILTI	212	238	LHBsAg	B cell epitopes
7332	SOISSHSPTCCPPICPGYRW	317	376	LHBsAg	B cell epitopes
11748	GYRWMCLRR	365	391	LHBsAg	B cell epitopes
15061	VIWMMWYWGR	386	415	LHBsAg	HLAI T cell epitopes
16814	CTIPAQGTSVFPSCCCTKPS	524	595	LHBsAg	HLAI T cell epitopes
	DGNC				
16815	CTIPAQGTSMFPSCCCTKPS	524	595	LHBsAg	HLAI T cell epitopes
	DGNC				
21242	FLWEWASA	635	658	LHBsAg	HLAI T cell epitopes
18802	CTKPTDGNC	569	595	LHBsAg	HLAII T cell epitopes
5191	TPARVTGGVF	151	180	Polymeras	HLAI T cell epitopes
15879	SGLPRYVARL	445	474	Polymeras	HLAI T cell epitopes
16751	GLSRYVARL	448	474	Polymeras	HLAI T cell epitopes
16753	GLSRYVARLS	448	477	Polymeras	HLAI T cell epitopes
16832	YIDDVVLGA	541	567	Polymeras	HLAI T cell epitopes
16833	YVDDVVLGA	541	567	Polymeras	HLAI T cell epitopes
19351	TYGRKLHLYSHPIILGFRKI	577	636	Polymeras	HLAI T cell epitopes
21070	LHLYSHPIILGFRKI	592	636	Polymeras	HLAI T cell epitopes
21116	KLHLYSHPI	595	621	Polymeras	HLAI T cell epitopes
24302	FLLSLGIHL	808	834	Polymeras	HLAI T cell epitopes
24943	KOCFRKLPVNRPIDW	937	981	Polymeras	HLAI T cell epitopes
27168	YPALMPLSACIQAKR	1042	1086	Polymeras	HLAI T cell epitopes
27169	QAFTFSPTYK	1051	1080	Polymeras	HLAI T cell epitopes
27285	KQAFTFSPTYKAFLC	1081	1125	Polymeras	HLAI T cell epitopes
27365	LCOVFADATPTGWGL	1171	1215	Polymeras	HLAI T cell epitopes
27878	YMDDVVLGA	1283	1309	Polymeras	HLAI T cell epitopes
32955	ILRGTSFVYV	1402	1431	Polymeras	HLAI T cell epitopes
34616	SLYADSPSV	1498	1524	Polymeras	HLAI T cell epitopes
226775	NVSIPWTHK	2445	2471	Polymeras	HLAI T cell epitopes
226786	KVGNFTGLY	2469	2495	Polymeras	HLAI T cell epitopes
226809	GLYSSTVPV	2487	2513	Polymeras	HLAI T cell epitopes
422990	VGPLTVNEKRRLKLI	2592	2636	Polymeras	HLAI T cell epitopes
422997	RHYLHTLWKAGILYK	2739	2783	Polymeras	HLAI T cell epitopes
423031	HTLWKAGILYK	2751	2783	Polymeras	HLAI T cell epitopes
423032	TLWKAGILYK	2754	2783	Polymeras	HLAI T cell epitopes
423036	ESTRSASFCGSPYSW	2787	2831	Polymeras	HLAI T cell epitopes
5191	TPARVTGGVF	151	180	Polymeras	HLAII T cell epitopes
7171	ESRLVVDFSQFSRGN	244	288	Polymeras	HLAII T cell epitopes
7230	VVDFSQFSR	262	288	Polymeras	HLAII T cell epitopes
8608	LQSLTNLLSSNLSWL	325	369	Polymeras	HLAII T cell epitopes
9815	SSNLSWLSLDVSAAF	349	393	Polymeras	HLAII T cell epitopes
15848	GVSRYVARL	415	441	Polymeras	HLAII T cell epitopes
15957	GLPRYVARL	448	474	Polymeras	HLAII T cell epitopes
16833	YVDDVVLGA	541	567	Polymeras	HLAII T cell epitopes
25650	ALMPYACI	1015	1041	Polymeras	HLAII T cell epitopes
30373	AANWILRGTSFVYVP	1390	1434	Polymeras	HLAII T cell epitopes
7161	VDKNPHNTTESRLVV	217	261	Polymeras	B cell epitopes
7162	LVVDFSQFSR	220	249	Polymeras	B cell epitopes
7171	ESRLVVDFSQFSRGN	244	288	Polymeras	B cell epitopes
23068	SAICSVVRR	649	675	Polymeras	B cell epitopes
51311	GATVELLSFLPSDF	1928	1972	PreC/C	HLAI T cell epitopes
56814	FLPSDFFPSI	1952	1981	PreC/C	HLAI T cell epitopes
59585	PSDFFPSVRDLLDTA	1958	2002	PreC/C	HLAI T cell epitopes
59786	SDFFPSVRDLLDTASALYR	1961	2020	PreC/C	HLAI T cell epitopes
61741	LLDTASALY	1988	2014	PreC/C	HLAI T cell epitopes
62477	YRDALESPEHCSPHHTA	2012	2062	PreC/C	HLAI T cell epitopes
62504	ALESPEHCSPHHTALROAIL	2021	2080	PreC/C	HLAI T cell epitopes
65148	LESQDHCSL	2024	2050	PreC/C	HLAI T cell epitopes
65509	PHHTALROAILCWGELMT	2048	2107	PreC/C	HLAI T cell epitopes
69398	TWVGNTLEDPASRDVVS	2108	2167	PreC/C	HLAI T cell epitopes
69474	WVGVNLEDPASRDVVS	2111	2170	PreC/C	HLAI T cell epitopes
69500	VGSNLEDPASRELVVSYVN	2114	2170	PreC/C	HLAI T cell epitopes
69524	GVNLEDPASRDL	2117	2152	PreC/C	HLAI T cell epitopes
71631	TNLEDPASRDVVS	2120	2164	PreC/C	HLAI T cell epitopes

71847	NLEDPASRD	2123	2152	PreC/C	HLAI T cell epitopes
74180	ASRDLVVSYVNTNMGLKF RQLLWFHISCLTFGRETVIE	2138	2254	PreC/C	HLAI T cell epitopes
75040	VVSYVNTNMGLKFRQL	2153	2200	PreC/C	HLAI T cell epitopes
76245	YVNTNMGLK	2162	2188	PreC/C	HLAI T cell epitopes
76370	YVNVNMGLK	2162	2188	PreC/C	HLAI T cell epitopes
79601	LWFHISCLMF	2201	2230	PreC/C	HLAI T cell epitopes
93224	GRETVIEYLVSFVW	2231	2275	PreC/C	HLAI T cell epitopes
93431	GRETVLEYLVSFVW	2231	2275	PreC/C	HLAI T cell epitopes
93536	RETVIEYLVSF	2234	2266	PreC/C	HLAI T cell epitopes
110917	VSGVWIRTPPA	2258	2293	PreC/C	HLAI T cell epitopes
178829	VSGVWIRTPPAYRPPNAPI	2258	2317	PreC/C	HLAI T cell epitopes
187197	LSTLPETTVVRRRGRSPRR RTPSPR	2318	2392	PreC/C	HLAI T cell epitopes
190409	STLPETTVVRR	2321	2353	PreC/C	HLAI T cell epitopes
190443	STLPETTVV	2321	2347	PreC/C	HLAI T cell epitopes
190455	STLPETTVVRRRGRSPRRR	2321	2380	PreC/C	HLAI T cell epitopes
190488	TVVRRRGRSPRRRTP	2339	2383	PreC/C	HLAI T cell epitopes
190509	TVVRRRGRSP	2339	2368	PreC/C	HLAI T cell epitopes
190556	RRRGRSPRRR	2348	2377	PreC/C	HLAI T cell epitopes
190568	RRRGRSPRRRTPSPRRRRS QSPRRRRSQSRESQC	2348	2449	PreC/C	HLAI T cell epitopes
190569	GRSPRRRTPSPRRRRSQSPR RRRSQSRESQC	2357	2449	PreC/C	HLAI T cell epitopes
190577	SPRRRTPSPRRRRSO	2363	2407	PreC/C	HLAI T cell epitopes
190589	PSPRRRRS	2381	2404	PreC/C	HLAI T cell epitopes
190596	SPRRRRSOSPRRRRS	2384	2428	PreC/C	HLAI T cell epitopes
191095	QSPRRRRSOSRESOC	2405	2449	PreC/C	HLAI T cell epitopes
47828	MDIDPYKEFGATVELLSFL	1901	1960	PreC/C	HLAII T cell epitopes
47829	DIDPYKEFGATVELLSFLPS DFFPSVRDLLDTASA	1904	2008	PreC/C	HLAII T cell epitopes
47830	DIDPYKEFGATVELL	1904	1948	PreC/C	HLAII T cell epitopes
47832	IDPYKEFGATVELLS	1907	1951	PreC/C	HLAII T cell epitopes
47833	DPYKEFGATVELLSF	1910	1954	PreC/C	HLAII T cell epitopes
47834	PYKEFGATVELLSFL	1913	1957	PreC/C	HLAII T cell epitopes
47836	YKEFGATVELLSFLP	1916	1960	PreC/C	HLAII T cell epitopes
48757	KEFGASVELL	1919	1948	PreC/C	HLAII T cell epitopes
49308	EFGATVELLSFLPSD	1922	1966	PreC/C	HLAII T cell epitopes
50118	FGATVELLSFLPSDF	1925	1969	PreC/C	HLAII T cell epitopes
52404	ATVELLSFLPSDFFPSV	1931	1981	PreC/C	HLAII T cell epitopes
53382	TVELLSFLPSDFFPS	1934	1978	PreC/C	HLAII T cell epitopes
53383	VELLSFLPSDFFPSV	1937	1981	PreC/C	HLAII T cell epitopes
53394	LLSFLPSDFFPSVRD	1943	1987	PreC/C	HLAII T cell epitopes
58876	LPSDFFPSV	1955	1981	PreC/C	HLAII T cell epitopes
60227	FFPSIRDLL	1967	1993	PreC/C	HLAII T cell epitopes
60229	FPSVRDLLDTASALYREAL ESPEHCSPHHTA	1970	2062	PreC/C	HLAII T cell epitopes
61746	LYREALESPEHCSPHHTAL	2009	2074	PreC/C	HLAII T cell epitopes
65475	PHHTALRQAI	2048	2077	PreC/C	HLAII T cell epitopes
67204	LCWGELMTLATWVGVN EDPASRD	2078	2152	PreC/C	HLAII T cell epitopes
67300	LCWGELMTLATWVGVN	2078	2128	PreC/C	HLAII T cell epitopes
68276	VCWGELMNL	2078	2104	PreC/C	HLAII T cell epitopes
68599	CWGELMTLATWVGVNLE	2081	2155	PreC/C	HLAII T cell epitopes
70928	VNLEDPASRD	2120	2152	PreC/C	HLAII T cell epitopes
70929	VNLEDPASRDLVVSYVNT	2120	2200	PreC/C	HLAII T cell epitopes
71847	NLEDPASRD	2123	2152	PreC/C	HLAII T cell epitopes
73842	PHHTALRQAILCWGD	2135	2179	PreC/C	HLAII T cell epitopes
73843	PHHTALRQAILCWGDLMN	2135	2194	PreC/C	HLAII T cell epitopes
75585	VSYVNTNMGLKFRQL	2156	2200	PreC/C	HLAII T cell epitopes
93536	RETVIEYLVSF	2234	2266	PreC/C	HLAII T cell epitopes
48337	KEFGATVELLSFLPS	1919	1963	PreC/C	B cell epitopes
55712	FLPADFFPSV	1952	1981	PreC/C	B cell epitopes

55713	FLPSDFFPSV	1952	1981	PreC/C	B cell epitopes
60249	RDLLDTAAALYRDALESPE	1982	2041	PreC/C	B cell epitopes
61746	LYREALESPHCSPHHTAL	2009	2074	PreC/C	B cell epitopes
65360	HHHTALROAILCWGELMN	2048	2107	PreC/C	B cell epitopes
68600	CWGDMLTLATWVGTNLE	2081	2140	PreC/C	B cell epitopes
68618	GELMTLATW	2087	2113	PreC/C	B cell epitopes
71938	LEDPASRDLVVSY	2126	2164	PreC/C	B cell epitopes
72649	LEDPASRDLVVSYV	2126	2167	PreC/C	B cell epitopes
73843	PHHTALRQAILCWGDLMN	2135	2194	PreC/C	B cell epitopes
75662	SYVNTNMGLKFRQLLWFH	2159	2254	PreC/C	B cell epitopes
	ISCLTFGRETVIEWY				
79531	NVNMGLKIRO	2168	2197	PreC/C	B cell epitopes
79549	KFROLLWFHISCLTFGRET	2186	2254	PreC/C	B cell epitopes
79577	LLWFHISCLTFGRETVIEWY	2198	2257	PreC/C	B cell epitopes
79583	LWFHISCLTFGRETVIEWYLV	2201	2260	PreC/C	B cell epitopes
79594	LWFHISCLTF	2201	2230	PreC/C	B cell epitopes
79613	HISCLTFGR	2210	2236	PreC/C	B cell epitopes
79654	CLTFGRETIV	2219	2245	PreC/C	B cell epitopes
79672	CLTFGRETVIEWY	2219	2254	PreC/C	B cell epitopes
79673	LTFGRETVIEWYLVSF	2222	2266	PreC/C	B cell epitopes
96088	VLEYLVSFV	2243	2272	PreC/C	B cell epitopes
96630	EYLVSFVWIRTPPA	2249	2293	PreC/C	B cell epitopes
96862	EYLVSFVW	2249	2275	PreC/C	B cell epitopes
97104	LVSFVWIR	2255	2281	PreC/C	B cell epitopes
180906	SFVWIRTPPAYRPPNAPIL	2261	2320	PreC/C	B cell epitopes
180913	FGVWIRTPPAYR	2264	2299	PreC/C	B cell epitopes
180914	VWIRTPPAYR	2270	2299	PreC/C	B cell epitopes
180915	WIRTPPAYR	2273	2299	PreC/C	B cell epitopes
180916	IRTPPAYRPPNAPILSTLPET	2276	2344	PreC/C	B cell epitopes
180917	IRTPPAYRPPNAPILSTLPET	2276	2338	PreC/C	B cell epitopes
180928	PAYRPPNAPIL	2288	2320	PreC/C	B cell epitopes
180929	AYRPPNAPILSTLPE	2291	2335	PreC/C	B cell epitopes
180930	YRPPNAPILSTLPETT	2294	2341	PreC/C	B cell epitopes
56900	FLPPDFFPSV	1952	1981	PreC/C	HLAII T cell epitopes
56900	FLPPDFFPSV	1952	1981	PreC/C	B cell epitopes
46480	ISCSCPTVQASKLCLGWLW	1841	1906	PreC/C	HLAI T cell epitopes
	GMD				
50253	FGATVELLSFLPSDFFPSV	1925	1981	PreC/C	HLAI T cell epitopes
58122	FLPADFFPSI	1952	1981	PreC/C	HLAI T cell epitopes
61745	PHHTALRQAIVCWGELMT	1997	2056	PreC/C	HLAI T cell epitopes
69715	GGNLEDPISRDLVVSYVNT	2117	2173	PreC/C	HLAI T cell epitopes
190466	STLPETTIVVRQ	2321	2353	PreC/C	HLAI T cell epitopes
46927	SCPTVQASKLCLGWLWG	1850	1900	PreC/C	HLAII T cell epitopes
47826	SKLCLGWLWMD	1871	1906	PreC/C	HLAII T cell epitopes
47827	LGWLWMDIDIPYKEF	1883	1927	PreC/C	HLAII T cell epitopes
57129	FLPVDFPSV	1952	1981	PreC/C	HLAII T cell epitopes
66988	PHHTALRQAILCWGDLMN	2048	2107	PreC/C	HLAII T cell epitopes
67096	PHHTALRQAILCWGELMN	2048	2107	PreC/C	HLAII T cell epitopes
67203	PHHTALROAVLCWGELMT	2048	2107	PreC/C	HLAII T cell epitopes
74445	RDLVVSYVNTNVGLKFRQ	2144	2203	PreC/C	HLAII T cell epitopes
46013	MQLFHLCLIISCTCPTVQAS	1814	1873	PreC/C	B cell epitopes
46927	SCPTVQASKLCLGWLWG	1850	1900	PreC/C	B cell epitopes
57784	FLPNDFPSV	1952	1981	PreC/C	B cell epitopes
66895	PHHTALRQAILCWGDLMN	2048	2107	PreC/C	B cell epitopes
79521	VNTNMGLKFRQLLWFHIS	2165	2221	PreC/C	B cell epitopes
79546	TNVGLKFRQLLWFHISCLT	2171	2230	PreC/C	B cell epitopes
79561	FRQLLWFHISCLTFGRETVI	2189	2257	PreC/C	B cell epitopes
79609	FHISCLTFGRETVIEWYLVSF	2207	2269	PreC/C	B cell epitopes
79677	TFGRETVIEWYLVSFVWIR	2225	2281	PreC/C	B cell epitopes
180919	PPAYRPPNAPILSTL	2285	2329	PreC/C	B cell epitopes
180931	ILSTLPETTIV	2315	2344	PreC/C	B cell epitopes
58234	FLPSDFLPSV	1952	1981	PreC/C	B cell epitopes

note: LHBsAg, large HBsAg; PreC/C, precore/core.

Table S3 dN/dS ratios of genome, pol, HbxAg, PreC/C and LHBsAg.

Groups	Patients		dN/dS			
	No	Genome	Pol	HBxAg	PreC/C	LHBsAg
Experimental	d10	0.7288	0.626	0.0001	0.0001	425.2716
Experimental	d10	0.4379	0.0001	0.364	0.0001	339.4327
Experimental	d10	0.0001	10.397	0.3556	0.0001	0.0001
Experimental	d10	0.6569	999	0.3625	0.0001	0.4561
Experimental	d10	0.8765	1.2549	0.0001	0.0001	339.6112
Experimental	d10	2.6121	1.2346	999	0.0001	7.0964
Experimental	d10	0.0001	8.3203	0.3084	0.0001	0.0001
Experimental	d10	0.0001	6.6045	0.3107	0.0001	0.0001
Experimental	d10	1.3149	0.4171	0.3064	870.3481	425.6478
Experimental	d15	0.0001	8.4696	0.3116	0.0508	0.0001
Experimental	d15	0.0001	8.5683	0.3166	0.1047	0.0001
Experimental	d15	0.0001	12.9322	0.3128	0.0852	0.0001
Experimental	d15	0.0001	7.7717	0.3148	0.251	0.0001
Experimental	d15	0.0001	7.5559	0.3152	0.037	0.0001
Experimental	d15	0.0001	9.2665	0.3115	0.0881	0.0001
Experimental	d15	1.0444	0.5089	0.3182	0.56	487.2994
Experimental	d15	0.6654	0.3098	1.3778	0.0001	6.6585
Experimental	d2	0.4333	0.1648	993.5894	0.0761	422.4457
Experimental	d2	0.0001	6.7914	0.3008	0.0629	0.0001
Experimental	d2	173.0408	13.7259	0.3091	875.8592	0.0001
Experimental	d2	1.311	999	0.0001	0.0804	338.4502
Experimental	d2	0.8708	0.8308	0.4575	0.8376	337.7533
Experimental	d23	1.0202	0.4146	999	0.0001	485.2943
Experimental	d23	0.0001	0.0001	0.3429	0.1028	0.0001
Experimental	d23	0.0001	0.0001	0.3377	0.0001	0.0001
Experimental	d23	0.0001	0.0001	0.3398	0.0001	0.0001
Experimental	d23	326.9184	999	996.5506	873.0142	425.0353
Experimental	d23	0.0001	0.0001	0.3262	0.1159	0.2285
Experimental	d23	0.0001	0.0001	0.334	0.0988	0.0001
Experimental	d23	2.1868	999	998.535	0.0001	0.919
Experimental	d23	0.2621	0.2766	0.3364	0.0695	534.7221
Experimental	d23	0.1456	0.1382	0.3455	0.0001	1.3785
Experimental	d23	0.6567	999	0.3234	0.1025	0.0001
Experimental	d23	1.4605	2.5031	0.3355	0.1036	0.4591
Experimental	d23	390.536	999	999	0.0001	0.0001
Experimental	d23	0.4367	0.4142	0.4589	0.4184	0.0001
Experimental	d23	0.4382	999	0.3225	0.0436	486.5935
Experimental	d23	1.1705	2.0873	997.9338	0.1262	0.2285
Experimental	d23	0.6578	0.8339	999	0.1243	425.1518
Experimental	d23	1.3162	0.8345	999	0.0631	0.0001
Experimental	d23	2.6322	0.833	998.6699	0.1581	0.0001
Experimental	d24	1.7552	0.4175	0.3134	863.7041	426.0316
Experimental	d24	222.284	811.4317	0.3112	0.0001	340.8202
Experimental	d24	0.0001	0.0001	0.3101	999	0.0001
Experimental	d24	257.6399	1.2483	0.3188	0.0001	0.0001
Experimental	d24	0.0001	1.6619	0.3423	0.0001	0.0001
Experimental	d24	0.0001	1.6666	0.3422	0.0001	0.0001
Experimental	d24	0.0001	0.0001	0.3409	0.0001	0.0001
Experimental	d24	0.7311	999	0.0001	864.7285	0.0001
Experimental	d24	0.5847	0.2778	0.3148	0.0001	426.2213
Experimental	d24	0.6577	1.2522	0.3094	0.0001	0.0001
Experimental	d24	222.2845	810.7659	0.3096	0.0001	340.517
Experimental	d24	1.7548	999	0.0001	0.0001	426.133
Experimental	d7	0.5235	0.8238	0.0001	0.1395	0.4602
Experimental	d7	0.4365	999	0.3128	0.0001	0.0001
Experimental	d7	0.3491	0.412	0.4584	0.1132	0.0001
Experimental	d7	2.183	999	0.3186	0.0743	0.4605
Experimental	d7	0.727	2.4769	0.0001	0.1043	0.0001
Experimental	d7	0.6011	0.2064	0.3478	0.4192	426.4093
Experimental	d7	0.421	0.2742	998.3971	876.5726	0.0001
Experimental	d7	1.32	999	0.3087	0.4189	0.0001
Experimental	d7	0.5222	0.5776	994.8217	0.1476	0.3643
Experimental	d7	0.6957	0.6855	999	0.174	0.6879
Experimental	d7	1.7474	1.0988	0.2276	0.1035	3.2281
Experimental	d7	1.0763	0.5464	0.0001	999	1.373
Control	cfq	0.0001	6.9379	0.3282	0.103	0.0001
Control	cfq	0.0001	4.5017	0.3377	0.1054	0.0001
Control	cfq	0.2186	0.0001	0.2266	0.1177	0.0001
Control	cfq	0.3282	0.416	0.0001	876.1373	0.0001

Control	cfq	0.4041	0.1039	0.0001	989.1077	425.7829
Control	cfq	0.7662	0.4162	996.2854	0.6405	0.0001
Control	cfq	1.1697	0.6955	0.2577	0.0501	486.1918
Control	cfq	0.3749	0.4161	0.0001	878.2697	0.9184
Control	cfq	1.3152	0.4165	998.2267	874.4811	0.0001
Control	cfq	1.7562	0.6939	999	876.5491	534.0365
Control	cfq	307.1197	999	0.3384	877.5599	340.1642
Control	kxy	1.3118	999	0.4597	0.193	0.0001
Control	kxy	0.8742	0.4123	999	0.1961	1.8528
Control	kxy	2.1902	999	0.3602	883.6503	0.4607
Control	kxy	0.0001	0.0001	0.34	0.2523	0.0001
Control	kxy	0.0001	0.0001	0.3442	0.2292	0.0001
Control	kxy	0.0001	0.0001	0.3417	0.2784	0.0001
Control	kxy	1.6052	999	0.3545	0.2127	1.3859
Control	kxy	0.0001	0.0001	0.3629	0.087	0.0001
Control	kxy	0.0001	0.0001	0.3554	0.1593	0.0001
Control	lmx	0.0001	0.0001	0.3228	0.1875	0.0001
Control	lmx	1.0912	1.0428	0.3289	0.1575	0.0001
Control	lmx	172.3826	0.0001	0.3485	877.8005	0.0001
Control	lmx	0.0001	17.8258	0.3541	0.0248	0.0001
Control	lmx	0.0001	0.0001	0.3325	0.1897	0.0001
Control	lmx	0.0001	0.0001	0.3426	0.1399	0.0001
Control	lmx	0.0001	11.1316	0.3445	0.1584	0.0001
Control	lmx	0.0001	0.0001	0.3102	0.1132	0.0001
Control	lmx	0.0001	0.0001	0.3129	0.1647	0.0001
Control	lmx	254.1254	999	0.3431	0.1722	338.2032
Control	lmx	1.3088	0.0001	998.3381	999	338.7426
Control	lmx	0.2175	807.6278	0.0001	0.0001	0.0001
Control	lyl	256.147	999	0.4189	0.0001	339.2307
Control	lyl	0.0001	0.0001	0.4199	0.0001	0.0001
Control	lyl	0.4367	0.0001	0.4136	0.0001	0.0001
Control	lyl	0.6548	807.5884	999	0.0001	0.2263
Control	lyl	0.3734	2.0821	0.4096	0.0001	0.4529
Control	lyl	0.2181	999	0.4015	0.0001	338.6178
Control	lyl	0.0001	9.8987	0.4018	0.0001	0.0001
Control	lyl	0.0001	13.9145	0.4097	0.0001	0.0001
Control	lyl	1.3103	0.4169	0.4047	0.1082	423.5669
Control	lyl	0.0001	8.523	0.4057	872.326	0.0001
Control	wr	0.0001	3.0271	0.3051	0.1253	0.0001
Control	wr	0.0001	47.2565	0.3089	0.0567	0.0001
Control	wr	0.0001	2.6024	0.3039	0.0657	0.0001
Control	wr	0.7317	0.4184	997.1649	0.1035	424.8489
Control	wr	0.4385	0.4183	0.9132	0.1093	0.0001
Control	wr	0.878	0.0001	995.74	0.0982	339.7319
Control	wr	2.1963	1.6752	0.2948	0.1625	340.0721
Control	wr	0.0001	29.5669	0.3113	0.142	0.0001
Control	wr	0.0001	28.9053	0.3073	0.1442	0.0001
Control	wr	0.4387	0.1043	0.3093	999	485.1787
Control	wr	1.757	1.6754	0.3022	876.2383	0.4548
Control	wr	0.8779	0.4182	0.3105	0.1103	339.7
Control	wr	0.548	0.2782	999	0.0975	0.4557
Control	wr	0.0001	13.7643	0.3101	0.0677	0.0001
Control	wr	0.4386	0.0001	0.3086	0.0001	339.6812
Control	xdh	0.0001	8.6739	0.322	0.1274	0.0001
Control	xdh	0.0001	8.1242	0.3177	0.0842	0.0001
Control	xdh	0.0001	11.8047	0.3221	0.0001	0.0001
Control	xdh	0.0001	9.329	0.315	0.0758	0.0001
Control	xdh	0.0001	0.3086	0.3186	0.1182	0.0001
Control	xdh	0.0001	12.5591	0.3197	0.1094	0.0001
Control	xdh	0.0001	0.0001	0.3155	0.071	0.0001
Control	xdh	0.0001	7.7991	0.3107	0.0001	0.0001
Control	xdh	0.2189	0.4178	0.0001	0.0727	0.0001
Control	xdh	0.8769	999	0.324	0.0614	0.0001
Control	xdh	0.2642	0.8379	0.0001	0.0001	0.1522

Table S4 Summary of positive selection analyses for genes LHBsAg, HBxAg, PreC/C and Pol.

Gene	LHBsAg	HBxAg	PreC/C	Pol
Model 1				
lnL	-4900.388	-1997.998	-2309.669	-10905.244
d_N/d_S (p_0)	0.099(0.470)	0.047(0.511)	0.095(0.693)	0.118(0.696)
d_N/d_S (p_1)	1.000(0.51)	1.000(0.489)	1.000(0.307)	1.000(0.304)
Model 2				
lnL	-4898.999	-1986.074626	-2308.911	-10892.446
d_N/d_S (p_0)	0.23(0.667)	0.11(0.532)	0.113(0.713)	0.138(0.71)
d_N/d_S (p_1)	1.000(0.000)	1.000(0.379)	1.000(0.274)	1.000(0.267)
d_N/d_S (p_2)	1.412(0.333)	4.148(0.09)	3.41(0.013)	3.401(0.023)
$2\Delta\ln L(\text{LRT})$ (2vs1)	2.778	23.846748	1.516	25.596
<i>P</i> Value	0.096	1.04E-06	0.218	4.21E-07
Positively selected sites*		36A,130K,131V		803R,841R
Model 7				
lnL	-4900.904	-1998.123	-2309.669	-10910.344
<i>p</i>	0.109	0.02	0.182	0.211
<i>q</i>	0.075	0.017	0.314	0.323
Model 8				
lnL	-4898.959	-1983.569	-2308.308	-10892.589
<i>p</i>	7.762	0.237	0.323	0.453
<i>q</i>	24.354	0.278	0.658	0.911
p_0	0.677	0.901	0.979	0.953
d_N/d_S (p_1)	1.427(0.323)	4.016(0.099)	3.1(0.021)	2.726(0.047)
$2\Delta\ln L(\text{LRT})$ (8vs7)	3.89	29.108	2.722	35.51
<i>P</i> Value	0.048	6.85E-08	0.099	2.54E-09
Positively selected sites*	300T	36A,44L,127V,130K,131V	159P	136Y,237Q,251P,480N,613Q,615I,713Q,803R,841R

*:BEB>0.9

D23	1679	G	20	20	0	0	0	0
D23	1708	T	20	0	1	0	0	0
D23	1719	G	20	0	0	0	20	0
D23	1721	A	20	0	0	20	0	0
D23	1731	T	20	0	1	0	0	0
D23	1762	A	20	0	0	0	20	0
D23	1766	T	20	0	20	0	0	0
D23	1768	A	20	0	0	0	20	0
D23	1778	A	20	0	0	2	0	0
D23	1790	T	20	1	0	0	0	0
D23	1805	A	20	0	0	2	0	0
D23	1846	T	20	20	0	0	0	0
D23	1863	T	20	0	1	0	0	0
D23	1896	A	20	0	0	19	0	0
D23	1913	A	20	0	20	0	0	0
D23	1922	C	20	0	0	20	0	0
D23	1923	C	20	20	0	0	0	0
D23	1930	A	20	0	0	1	0	0
D23	1933	A	20	0	0	0	20	0
D23	1963	T	20	0	1	0	0	0
D23	1966	C	20	0	0	0	1	0
D23	1979	G	20	20	0	0	0	0
D23	1981	T	20	0	1	0	0	0
D23	1984	T	20	19	0	1	0	0
D23	1999	C	20	0	0	0	2	0
D23	2065	C	20	3	0	0	0	0
D23	2078	G	20	0	20	0	0	0
D23	2096	A	20	0	0	1	0	0
D23	2107	A	20	0	20	0	0	0
D23	2134	T	20	0	20	0	0	0
D23	2158	A	20	0	20	0	0	0
D23	2159	A	20	0	0	1	0	0
D23	2184	T	20	1	0	0	0	0
D23	2189	A	20	0	1	0	0	0
D23	2202	T	20	0	1	1	0	0
D23	2209	C	20	0	0	0	20	0
D23	2216	T	20	0	1	0	0	0
D23	2227	T	20	0	0	1	0	0
D23	2299	A	20	0	0	2	0	0
D23	2304	C	20	1	0	0	0	0
D23	2323	A	20	0	0	0	2	0
D23	2410	A	20	0	0	20	0	0
D23	2430	A	20	0	0	2	0	0
D23	2451	A	20	0	0	1	0	0
D23	2456	C	20	0	0	0	3	0
D23	2468	T	20	0	20	0	0	0
D23	2489	G	20	2	0	0	0	0
D23	2537	T	20	0	20	0	0	0
D23	2541	T	20	0	1	0	0	0
D23	2558	G	20	20	0	0	0	0
D23	2560	G	20	20	0	0	0	0
D23	2564	A	20	0	0	20	0	0
D23	2573	C	20	0	0	0	20	0
D23	2582	C	20	0	0	0	20	0
D23	2590	A	20	0	0	1	0	0
D23	2591	C	20	0	0	0	20	0
D23	2594	G	20	20	0	0	0	0
D23	2603	C	20	0	0	0	20	0
D23	2612	C	20	0	0	0	20	0
D23	2622	A	20	0	0	1	0	0
D23	2627	A	20	0	0	1	0	0
D23	2660	C	20	0	0	0	20	0
D23	2681	A	20	0	0	20	0	0
D23	2684	T	20	0	20	0	0	0
D23	2699	T	20	1	0	19	0	0
D23	2708	T	20	0	0	1	0	0
D23	2712	C	20	0	0	0	19	0
D23	2732	T	20	0	20	0	0	0
D23	2740	G	20	0	0	0	1	0
D23	2741	A	20	0	0	20	0	0
D23	2771	C	20	0	0	0	19	0
D23	2849	T	20	0	1	0	0	0
D23	2856	T	20	0	1	0	0	0
D23	2875	A	20	0	20	0	0	0
D23	2890	A	20	0	0	1	0	0
D23	2898	G	20	0	1	0	19	0
D23	2900	T	20	0	0	1	0	0
D23	2928	T	20	0	1	0	0	0
D23	2952	A	20	0	0	1	0	0
D23	2958	T	20	0	20	0	0	0
D23	2995	G	20	1	0	0	0	0
D23	3000	C	20	0	0	0	20	0
D23	3008	C	20	20	0	0	0	0
D23	3013	A	20	0	0	3	0	0
D23	3046	T	20	0	1	0	0	0
D23	3051	T	20	0	20	0	0	0
D23	3057	C	20	20	0	0	0	0
D23	3064	A	20	0	0	20	0	0
D23	3066	T	20	0	1	0	0	0
D23	3084	G	20	0	0	0	20	0
D23	3099	A	20	0	1	0	0	0
D23	3105	T	20	20	0	0	0	0
D23	3120	G	20	20	0	0	0	0
D23	3150	A	20	0	0	2	0	0
D23	3160	C	20	0	0	0	1	0
D23	3172	T	20	0	1	0	0	0
D23	3180	T	20	0	2	0	0	0
D23	3204	T	20	0	20	0	0	0
D02	6	C	16	0	0	0	1	0
D02	9	C	16	0	0	0	1	0
D02	10	C	16	0	0	5	11	0
D02	19	A	16	0	0	0	11	0
D02	24	T	16	1	0	0	0	0
D02	29	G	16	10	0	0	0	0
D02	36	G	16	16	0	0	0	0
D02	176	T	16	0	1	0	0	0
D02	189	T	16	0	0	11	0	0
D02	213	T	16	0	1	0	0	0
D02	241	G	16	10	0	0	0	0
D02	285	G	16	1	0	0	0	0
D02	323	A	16	0	0	1	0	0
D02	333	A	16	0	11	0	0	0
D02	339	C	16	0	0	0	11	0
D02	382	T	16	0	1	0	0	0
D02	387	G	16	11	0	0	0	0
D02	482	A	16	0	11	0	0	0
D02	495	C	16	0	0	0	1	0
D02	514	A	16	0	0	3	0	0
D02	522	C	16	0	0	0	2	0
D02	554	T	16	11	0	0	0	0
D02	558	C	16	0	0	0	8	0

D02	574	C	16	7	0	0	0	0
D02	587	G	16	8	0	0	0	0
D02	591	A	16	0	1	0	0	0
D02	636	A	16	0	0	0	7	0
D02	667	C	16	0	0	0	3	0
D02	670	C	16	1	0	0	0	0
D02	686	C	16	0	0	0	1	0
D02	688	A	16	0	16	0	0	0
D02	700	G	16	1	0	0	0	0
D02	705	T	16	0	0	1	0	0
D02	717	C	16	0	0	0	1	0
D02	739	A	16	0	0	1	0	0
D02	748	G	16	8	0	0	0	0
D02	749	T	16	1	0	0	0	0
D02	750	G	16	8	0	0	0	0
D02	770	T	16	0	8	0	0	0
D02	771	A	16	0	0	1	0	0
D02	798	T	16	0	1	0	0	0
D02	832	T	16	0	3	0	0	0
D02	837	C	16	0	0	0	8	0
D02	838	T	16	0	16	0	0	0
D02	849	T	16	5	0	0	0	0
D02	853	A	16	0	5	0	0	0
D02	912	A	16	0	0	8	0	0
D02	927	A	16	0	0	1	0	0
D02	942	G	16	15	0	0	0	0
D02	970	C	16	0	0	0	1	0
D02	981	G	16	0	1	0	0	0
D02	987	A	16	0	0	0	1	0
D02	994	A	16	0	6	0	0	0
D02	1000	T	16	0	0	2	0	0
D02	1009	C	16	0	0	0	16	0
D02	1029	T	16	0	15	0	0	0
D02	1042	T	16	0	1	0	0	0
D02	1044	C	16	0	0	0	16	0
D02	1077	A	16	0	10	0	0	0
D02	1095	T	16	0	1	0	0	0
D02	1124	A	16	0	0	16	0	0
D02	1125	C	16	0	0	0	16	0
D02	1126	A	16	0	1	0	0	0
D02	1128	A	16	0	6	0	0	0
D02	1135	A	16	0	0	6	0	0
D02	1139	A	16	0	2	0	0	0
D02	1173	G	16	14	1	0	0	0
D02	1175	A	16	0	0	16	0	0
D02	1218	C	16	0	0	0	1	0
D02	1252	T	16	0	0	16	0	0
D02	1254	T	16	0	0	1	0	0
D02	1278	A	16	0	0	1	0	0
D02	1287	T	16	0	16	0	0	0
D02	1306	A	16	0	16	0	0	0
D02	1320	C	16	16	0	0	0	0
D02	1321	C	16	2	0	0	0	0
D02	1337	A	16	0	1	0	0	0
D02	1350	T	16	0	0	1	0	0
D02	1362	C	16	0	0	0	16	0
D02	1365	A	16	0	1	0	0	0
D02	1375	T	16	0	1	0	0	0
D02	1381	C	16	0	0	0	1	0
D02	1417	T	16	0	1	0	0	0
D02	1425	T	16	0	16	0	0	0
D02	1432	C	16	0	0	0	1	0
D02	1437	A	16	0	0	16	0	0
D02	1450	G	16	1	0	0	0	0
D02	1480	A	16	0	0	1	0	0
D02	1485	T	16	0	16	0	0	0
D02	1497	C	16	0	0	0	16	0
D02	1499	G	16	11	0	0	0	0
D02	1508	T	16	15	0	0	0	0
D02	1511	T	16	1	0	0	0	0
D02	1544	T	16	16	0	0	0	0
D02	1553	T	16	0	1	0	0	0
D02	1575	C	16	0	0	0	1	0
D02	1583	A	16	0	0	1	0	0
D02	1632	A	16	0	16	0	0	0
D02	1635	G	16	16	0	0	0	0
D02	1637	C	16	15	0	1	0	0
D02	1647	G	16	1	0	0	0	0
D02	1652	G	16	3	0	0	0	0
D02	1655	T	16	0	2	0	0	0
D02	1657	A	16	0	0	1	0	0
D02	1691	C	16	0	0	0	1	0
D02	1742	G	16	14	0	0	2	0
D02	1747	A	16	0	5	0	0	0
D02	1748	G	16	0	0	0	9	0
D02	1751	G	16	0	0	0	8	0
D02	1752	A	16	0	0	1	1	0
D02	1753	T	16	5	11	0	0	0
D02	1762	A	16	0	0	0	16	0
D02	1763	G	16	1	0	0	0	0
D02	1766	C	16	0	0	0	10	0
D02	1768	T	16	11	0	0	0	0
D02	1769	C	16	0	0	0	16	0
D02	1773	C	16	0	0	0	8	0
D02	1820	A	16	0	16	0	0	0
D02	1846	A	16	0	0	0	1	0
D02	1853	T	16	0	1	0	0	0
D02	1862	G	16	0	0	0	1	0
D02	1896	G	16	11	0	0	0	0
D02	1899	G	16	1	0	0	0	0
D02	1917	A	16	0	0	0	1	0
D02	1944	T	16	0	1	0	0	0
D02	1961	T	16	11	0	0	0	0
D02	1962	C	16	1	0	0	0	0
D02	1966	T	16	0	1	0	0	0
D02	1975	G	16	8	0	0	0	0
D02	1983	G	16	11	0	0	0	0
D02	1984	G	16	16	0	0	0	0
D02	1987	C	16	0	0	0	1	0
D02	1990	T	16	0	9	0	0	0
D02	1991	C	16	10	0	0	1	0
D02	1999	C	16	2	0	0	0	0
D02	2003	T	16	11	0	0	0	0
D02	2011	C	16	0	0	16	0	0
D02	2035	A	16	0	0	16	0	0
D02	2037	A	16	0	0	1	0	0
D02	2038	A	16	0	0	1	0	0
D02	2044	T	16	0	9	0	0	0
D02	2053	C	16	0	0	0	7	0
D02	2074	T	16	16	0	0	0	0
D02	2075	G	16	16	0	0	0	0
D02	2083	T	16	0	5	0	0	0

D02	2086	G	16	0	0	0	11	0
D02	2089	T	16	0	0	16	0	0
D02	2091	A	16	0	0	1	0	0
D02	2097	T	16	10	0	1	0	0
D02	2098	G	16	0	0	0	11	0
D02	2109	C	16	1	0	0	0	0
D02	2120	A	16	0	0	5	0	0
D02	2126	T	16	0	1	0	0	0
D02	2131	A	16	0	11	0	0	0
D02	2145	G	16	11	0	0	0	0
D02	2150	T	16	5	0	0	0	0
D02	2160	G	16	1	0	0	0	0
D02	2176	T	16	0	8	0	0	0
D02	2191	C	16	0	0	0	16	0
D02	2198	C	16	5	0	0	0	0
D02	2203	T	16	0	0	16	0	0
D02	2219	T	16	0	1	0	0	0
D02	2239	A	16	0	16	0	0	0
D02	2245	C	16	0	0	0	16	0
D02	2260	G	16	16	0	0	0	0
D02	2266	C	16	0	0	0	16	0
D02	2271	T	16	0	1	0	0	0
D02	2290	C	16	5	0	0	0	0
D02	2304	C	16	11	0	0	0	0
D02	2345	G	16	11	0	0	0	0
D02	2351	C	16	0	0	10	0	0
D02	2352	G	16	1	0	0	0	0
D02	2364	C	16	0	0	11	0	0
D02	2369	A	16	0	0	11	0	0
D02	2376	G	16	1	0	0	0	0
D02	2401	A	16	0	0	16	0	0
D02	2456	T	16	0	16	0	0	0
D02	2489	G	16	0	0	0	1	0
D02	2538	T	16	0	1	0	0	0
D02	2567	C	16	0	0	0	5	0
D02	2590	T	16	0	1	0	0	0
D02	2618	A	16	0	0	16	0	0
D02	2621	A	16	0	0	16	0	0
D02	2636	C	16	0	0	0	16	0
D02	2642	T	16	0	1	0	0	0
D02	2659	A	16	0	8	0	0	0
D02	2660	C	16	3	0	2	0	0
D02	2663	T	16	0	0	1	0	0
D02	2675	A	16	0	0	16	0	0
D02	2681	G	16	16	0	0	0	0
D02	2711	G	16	16	0	0	0	0
D02	2720	T	16	0	10	0	0	0
D02	2810	C	16	0	0	0	16	0
D02	2853	A	16	0	0	1	0	0
D02	2854	G	16	8	0	0	1	0
D02	2865	C	16	2	0	0	0	0
D02	2875	A	16	0	0	1	0	0
D02	2946	A	16	0	0	5	0	0
D02	2973	G	16	0	0	0	5	0
D02	3040	T	16	0	5	0	0	0
D02	3045	G	16	0	0	0	5	0
D02	3051	T	16	0	5	0	0	0
D02	3057	T	16	5	0	0	0	0
D02	3059	A	16	0	0	1	0	0
D02	3087	G	16	5	0	0	0	0
D02	3088	G	16	0	0	0	5	0
D02	3099	T	16	5	0	0	0	0
D02	3144	G	16	1	0	0	0	0
D02	3154	A	16	0	0	4	0	0
D02	3166	C	16	0	0	0	1	0
D02	3183	A	16	0	0	11	0	0
D02	3196	C	16	0	0	0	1	0
D02	3198	T	16	11	0	0	0	0
D02	3209	A	16	0	0	11	0	0

Table S6 Amino acid variations for A epitope (aa124–aa147).

Experimental group	Genotype C		Genotype I		
	Number	Control group	Number	Experimental group	Number
C124S	1	I126S	13	Y134N	11
T125M	3	I126G	2	P135L	8
I126T	24	Q129R	2	G145R	8
I126V	3	M133T	1	N146T	1
G130N	9	K141E	1		
G130R	5				
G130E	1				
T131I	1				
T131N	1				
M133T	5				
F134Y	14				
D144V	6				
D144A	3				

Number of substitutions per 100 amino acid

	Experimental group	Control group	p
a' determinant (aa 124-147)	4.76	0.91	0.0001

Table S7 Number of variation at Core Promoter and pre-Core region (nt1742-1900) in present study.

mutations	Experimental group (91)		Control group (87)		<i>p</i> value Chi-square test
	wild type	mutant type	wild type	mutant type	
A1762T	13	78	63	24	1.52064E-14
G1764A	13	78	58	29	2.92985E-12
T1753C	51	40	87	0	7.71992E-12
A1755C	76	15	87	0	0.00022653
G1742A	77	14	87	0	0.000410948
G1896A	77	14	87	0	0.000410948
T1802C	78	13	87	0	0.000742127
G1899A	78	13	87	0	0.000742127
T1768A	80	11	87	0	0.002392226
A1846T	77	14	85	2	0.005285676
C1773T	83	8	87	0	0.013586221
A1775G	76	15	82	5	0.042368534
T1861C	88	3	87	0	0.260341026
C1766T	81	10	72	15	0.324954096
C1799G	78	13	75	12	1

Table S8 Amino acid variations for genotype C HBV genome.

Genes	Position	Mutations	Experimental group (62 clones)		Control group (59 clones)		<i>p</i> value Chi-square test	Epitopes
			wild type	mutant type	wild type	mutant		
HBcAg	13	V13L	48	14	59	0	0	HLA I/II T,B
HBcAg	21	S21A	62	0	43	16	0	HLA I/II T,B
HBcAg	24	F24S	62	0	57	2	0.236	HLA I/II T,B
HBcAg	25	V25I	0	62	59	0	0	HLA I/II T,B
HBcAg	35	S35A	48	14	59	0	0	HLA I/II T,B
HBcAg	58	A58D	48	14	59	0	0	HLA II T,B
HBcAg	60	V60L	0	62	0	59	1	HLA I/II T,B
HBcAg	83	E83D	58	4	57	2	0.68	HLA I/II T,B
HBcAg	87	S87G/R	56	6	57	2	0.274	HLA I/II T,B
HBcAg	94	I94L	62	0	57	2	0.236	HLA I/II T,B
HBcAg	96	K96N	60	2	59	0	0.496	HLA I/II T,B
HBcAg	97	I97L	48	14	59	0	0	HLA I/II T,B
HBcAg	100	L100I	50	12	59	0	0	HLA I/II T,B
HBcAg	101	I101W	61	1	58	1	1	HLA I/II T,B
HBcAg	112	R112G	62	0	56	3	0.113	HLA I/II T,B
HBcAg	115	V115A	62	0	56	3	0.113	HLA I/II T,B
HBcAg	119	L119S	62	0	56	3	0.113	HLA I / II T
HBcAg	120	V120A	62	0	56	3	0.113	HLA I/II T,B
HBcAg	130	P130S/T	48	14	29	30	0.001	HLA I/II T,B
HBcAg	135	P135Q	61	1	58	1	1	HLA I/II T,B
HBcAg	148	V148I	48	14	59	0	0	HLA I/II T,B
HBcAg	152	R152Q	58	4	59	0	0.119	HLA I/II T,B
HBcAg	153	G153C	62	0	57	2	0.236	HLA I/II T,B
HBcAg	155	S155T	60	2	59	0	0.496	HLA II T,B
HBcAg	162	S162L	62	0	56	3	0.113	HLA I/II T,B
HBcAg	170	S170P	62	0	56	3	0.113	HLA II T,B
HBcAg	177	Q177R	60	2	54	5	0.265	HLA II T,B
HBcAg	180	E180G	62	0	44	15	0	HLA II T,B
HBxAg	4	R4G	56	6	59	0	0.028	B
HBxAg	5	L5V/P	16	46	29	30	0.009	B
HBxAg	21	V21F	58	4	59	0	0.119	B
HBxAg	29	S29P	0	62	0	59	1	B
HBxAg	30	V30I	62	0	41	18	0	B
HBxAg	32	S32R	58	4	59	0	0.119	B
HBxAg	35	G35R	54	8	59	0	0.006	B
HBxAg	36	G36S/A/T	0	62	12	47	0	B
HBxAg	38	P38S/L	60	2	59	0	0.496	B
HBxAg	42	L42S	0	62	12	47	0	B
HBxAg	43	S43P	55	7	44	15	0.059	B
HBxAg	47	A47T	54	8	44	15	0.105	B
HBxAg	48	N48D	0	62	0	59	1	B
HBxAg	59	P59S	62	0	57	2	0.236	HLA I T,B
HBxAg	61	C61R/Y	62	0	53	6	0.012	HLA II T,B
HBxAg	64	S64T	62	0	47	12	0	HLA II T,B
HBxAg	79	M79I	58	4	59	0	0.119	B
HBxAg	86	R86H/L/S	15	47	41	18	0	B
HBxAg	94	Y94H	0	62	0	59	1	HLA I T,B
HBxAg	95	K95N	62	0	45	14	0	HLA I/II T,B
HBxAg	96	R96K/G	60	2	59	0	0.496	HLA I/II T,B
HBxAg	101	S101P/A	52	10	44	15	0.263	HLA I/II T,B
HBxAg	112	F112S	58	4	59	0	0.119	HLA II T,B
HBxAg	116	V116L	29	33	44	15	0.003	HLA I/II T,B
HBxAg	123	L123S	62	0	41	18	0	HLA I/II T,B
HBxAg	127	I127T	33	29	59	0	0	HLA II T,B
HBxAg	130	K130M	13	49	41	18	0	HLA II T,B
HBxAg	131	I131V/T	49	13	35	24	0.029	HLA II T,B
HBxAg	132	Y132F	0	62	17	42	0	HLA II T,B
LHBsAg	1	M1T	61	1	58	1	1	
LHBsAg	10	K10Q	4	58	12	47	0.032	HLA II T
LHBsAg	14	T14S	62	0	54	5	0.025	HLA II T
LHBsAg	27	D27G	48	14	41	18	0.41	HLA I T,B
LHBsAg	35	G35R	62	0	56	3	0.113	HLA I T,B
LHBsAg	41	P41S	62	0	47	12	0	B
LHBsAg	50	D50G	60	2	59	0	0.496	
LHBsAg	51	H51Q	47	15	41	18	0.541	
LHBsAg	54	A54E	15	47	30	29	0.003	
LHBsAg	55	N55D/E	54	8	59	0	0.006	
LHBsAg	60	A60V	37	25	41	18	0.342	B

LHBsAg	62	A62S	47	15	41	18	0.541	B
LHBsAg	67	F67L	60	2	59	0	0.496	
LHBsAg	73	S73G	20	42	30	29	0.044	B
LHBsAg	77	W77S	52	10	59	0	0.001	HLA I T,B
LHBsAg	88	V88M/A	57	5	59	0	0.058	B
LHBsAg	90	A90V	49	13	44	15	0.667	B
LHBsAg	98	N98T	60	2	59	0	0.496	
LHBsAg	102	G102R	60	2	59	0	0.496	
LHBsAg	105	P105S	57	5	59	0	0.058	B
LHBsAg	120	M120T/V	48	14	59	0	0	HLA I/II T,B
LHBsAg	125	T125S	47	15	41	18	0.541	HLA I/II T,B
LHBsAg	128	H128L	48	14	59	0	0	HLA I/II T,B
LHBsAg	130	A130T	49	13	59	0	0	HLA I/II T,B
LHBsAg	132	L132Q	48	14	59	0	0	HLA I/II T,B
LHBsAg	133	D133G	62	0	57	2	0.236	HLA I/II T,B
LHBsAg	141	F141C	60	2	59	0	0.496	HLA II T,B
LHBsAg	152	N152S	59	3	58	1	0.619	HLA II T,B
LHBsAg	158	A158V	55	7	59	0	0.013	HLA II T,B
LHBsAg	161	I161V	62	0	41	18	0	HLA II T,B
LHBsAg	164	I164V	60	2	59	0	0.496	B
LHBsAg	165	F165S	48	14	59	0	0	
LHBsAg	168	T168I	49	13	59	0	0	
LHBsAg	173	A173P	14	48	0	59	0	HLA I T
LHBsAg	173	A173L	48	14	59	0	0	HLA I T
LHBsAg	174	N174S	62	0	55	4	0.054	HLA I T
LHBsAg	177	N177S	16	46	41	18	0	HLA I T/HLA II T
LHBsAg	178	T178I	48	14	59	0	0	HLA I T/HLA II T
LHBsAg	182	F182L	60	2	59	0	0.496	HLA I/II T,B
LHBsAg	184	G184R/K/T	46	16	59	0	0	HLA I/II T,B
LHBsAg	188	V188A	47	15	59	0	0	HLA I/II T,B
LHBsAg	194	F194S	60	2	59	0	0.496	HLA I T,B
LHBsAg	195	L195W	58	4	59	0	0.119	HLA I T,B
LHBsAg	195	L195S	60	2	59	0	0.496	HLA I T,B
LHBsAg	198	R198K	60	2	59	0	0.496	HLA I T,B
LHBsAg	208	S208P	62	0	57	2	0.236	HLA I T,B
LHBsAg	219	A219V/T	46	16	59	0	0	B
LHBsAg	220	P220S/T	46	16	59	0	0	B
LHBsAg	221	T221V/A	48	14	56	3	0.008	B
LHBsAg	223	P223R	48	14	59	0	0	B
LHBsAg	227	L227S	13	49	30	29	0.001	B
LHBsAg	235	S235L	57	5	53	6	0.759	B
LHBsAg	236	P236L	52	10	58	1	0.009	B
LHBsAg	237	T237I	60	2	59	0	0.496	B
LHBsAg	242	T242I	34	28	12	47	0	B
LHBsAg	250	C250Y	55	7	59	0	0.013	HLA I T
LHBsAg	254	F254L	59	3	59	0	0.244	HLA I T
LHBsAg	261	L261P	61	1	58	1	1	HLA I T
LHBsAg	269	L269W	60	2	59	0	0.496	HLA I T,B
LHBsAg	272	L272V	52	10	59	0	0.001	HLA I T,B
LHBsAg	273	D273G	61	1	56	3	0.356	HLA I T,B
LHBsAg	283	L283P	62	0	55	4	0.054	B
LHBsAg	284	L284I	53	9	59	0	0.003	B
LHBsAg	287	T287S/N/P	48	14	56	3	0.003	B
LHBsAg	296	K296R	48	14	59	0	0	HLA I T,B
LHBsAg	299	T299M	59	3	59	0	0.244	HLA I/II T,B
LHBsAg	300	I300V/T/G/S	34	28	44	15	0.036	HLA I/II T,B
LHBsAg	301	G301R/N	48	14	59	0	0	HLA I/II T,B
LHBsAg	303	Q303R	62	0	57	2	0.236	HLA I/II T,B
LHBsAg	307	M307T	57	5	58	1	0.208	HLA II T,B
LHBsAg	308	F308Y	48	14	59	0	0	HLA II T,B
LHBsAg	318	D318A/V	53	9	59	0	0.003	HLA I/II T,B
LHBsAg	323	C323R	62	0	56	3	0.113	
LHBsAg	333	A333G	48	14	59	0	0	HLA I T
LHBsAg	334	R334K	48	14	59	0	0	HLA I T
LHBsAg	336	L336Q	62	0	44	15	0	HLA I T
LHBsAg	342	V342A	47	15	59	0	0	HLA I T
LHBsAg	349	L349S	62	0	47	12	0	HLA I T
LHBsAg	351	V351A	62	0	56	3	0.113	HLA I T
LHBsAg	359	G359R	60	2	59	0	0.496	HLA I T
LHBsAg	368	A368V	0	62	13	46	0	
LHBsAg	371	M371T	60	2	59	0	0.496	HLA I T
LHBsAg	377	P377Q	58	4	59	0	0.119	HLA I T
LHBsAg	378	S378R	48	14	59	0	0	HLA I T

LHBsAg	381	N381S	48	14	59	0	0	HLA I T
LHBsAg	382	I382T	47	15	59	0	0	HLA I T
LHBsAg	384	S384N	47	15	41	18	0.541	HLA I T
LHBsAg	390	L390S	58	4	59	0	0.119	HLA I T
LHBsAg	398	V398A	58	4	59	0	0.119	
RT	7	S7A/T	0	62	0	59	1	
RT	9	H9Y	49	13	42	17	0.4	HLA I T
RT	13	N13H	34	28	41	18	0.134	
RT	16	I16T	60	2	59	0	0.496	
RT	18	R18K/N	46	16	59	0	0	
RT	19	T19A	60	2	59	0	0.496	
RT	23	V23A	62	0	57	2	0.236	
RT	38	T38A	48	14	47	12	0.827	HLA I T
RT	42	L42P	62	0	57	2	0.236	
RT	50	S50P	60	2	59	0	0.496	HLA I T
RT	53	S53N	48	14	59	0	0	HLA I T
RT	54	T54I/Y	46	16	59	0	0	
RT	55	H55R	48	14	56	3	0.008	
RT	88	F88S	59	3	59	0	0.244	
RT	91	I91L	35	27	41	18	0.188	
RT	106	S106C	51	11	59	0	0.001	HLA I T
RT	109	P109S	48	14	41	18	0.41	HLA I T
RT	118	T118N	53	9	59	0	0.003	
RT	121	N121K/I/T	48	14	56	3	0.008	
RT	122	F122I	14	48	13	46	0.558	
RT	123	N123D	48	14	59	0	0	
RT	124	Y124H	48	14	59	0	0	
RT	126	H126Y	62	0	47	12	0	
RT	128	T128A	62	0	41	18	0	
RT	129	M129L	49	13	59	0	0	
RT	129	M129V	57	5	59	0	0.058	
RT	131	D131N	48	14	59	0	0	
RT	134	D134G	60	2	57	2	1	
RT	134	D134E	61	1	46	13	0	
RT	135	T135S	0	62	12	47	0	
RT	138	R138K	48	14	59	0	0	
RT	139	N139H	53	9	59	0	0.003	
RT	145	L145M	60	2	59	0	0.496	
RT	157	L157S	62	0	56	3	0.113	HLA I T
RT	163	I163V	42	20	59	0	0	HLA I T
RT	170	P170S	59	3	59	0	0.244	
RT	193	R193K	60	2	59	0	0.496	
RT	213	S213T	48	14	59	0	0	HLA I T
RT	223	S223A	33	29	59	0	0	
RT	224	I224V	46	16	59	0	0	
RT	253	V253R/I	48	14	56	3	0.008	
RT	263	E263D	48	14	59	0	0	
RT	267	L267H/Q	14	48	27	32	0.008	
RT	269	I269L	14	48	36	23	0	
RT	271	P271Q	0	62	0	59	1	
RT	278	V278I	48	14	41	18	0.41	
RT	280	S280R	0	62	0	59	1	
RT	282	I282V	48	14	59	0	0	
RT	283	D283G	56	6	59	0	0.028	
RT	287	C287R	62	0	56	3	0.113	
RT	289	R289K	62	0	57	2	0.236	
RT	292	C292G	56	6	0	59	0	
RT	297	A297V	56	6	59	0	0.028	HLA I T

Table S9 Deletion , insertion and stop codon mutations of HBV quasiespecies observed in the present study.

Clinical spectrum	No. of Del , Ins or Stop codon mutations patients /total no.of patients	Patient ID (genotype)	No. of Del , Ins or Stop codon mutations /total no. of clones	Del/Insnt patterns(nt positions in fulllength HBV genome)	Del/Ins aa patterns (aa positions of related region)
Experimental group	6/6	D10(B)	1/13	nt1627	Del and frameshift HBxAg at aa85 with stop codon
			1/13	nt3165-3189	Del and frameshift LHBsAg at aa98-106 with stop codon, Del and frameshift Pol at aa278-286 with stop codon
			2/13	nt1896G-A	PreC/C W28*
		D15(C)	4/14	nt2971-2988	Del LHBsAg at aa42-47, Pol at aa223-228
			4/14	nt3141-3165	Del LHBsAg aa66-112, Pol at aa246-292
			4/14	nt41-43	LHBsAg R137*
			1/14	nt1376G-A	Pol W762*
			1/14	nt1374	Del HBxAg start codon,
			4/14	nt1610	Pol W840*
			1/14	nt1099-1584	Del Pol at aa670-831
		D02(I)	11/16	nt2863-3138	Del LHBsAg aa6-97, Pol aa186-277
			8/16	nt503-526	Del LHBsAg aa291-298, Pol aa471-478
			1/16	nt670G-A	LHBsAg W346*
			1/16	nt700G-A	LHBsAg W356*
			8/16	nt750G-A	LHBsAg W373*
			11/16	nt1896G-A	PreC/C W28*
		D23(C)	1/20	nt1896G-A	PreC/C W28*
		D24(C)	1/13	nt3077	Del and frameshift LHBsAg at aa77 with stop codon, Del and frameshift Pol at aa257 with stop codon
		D07(C)	2/15	nt3022G-T	LHBsAg G59*
			1/15	nt79	Del and frameshift LHBsAg at aa149 with stop codon, Del and frameshift Pol at aa329 with stop codon
Control group	5/6	CFQ(C)	1/14	nt2859G-A	LHBsAg W4*
			1/14	nt3208C-T	LHBsAg Q121*
			1/14	nt1421	Del and frameshift Pol at aa776 with stop codon, Del and frameshift HBxAg at aa16 with stop codon
			1/14	nt2109	Del and frameshift PreC/C at aa 98 with stop codon
			2/14	nt2132-2217	Del PreC/C aa107-134
			1/14	nt2102-2217	Del PreC/C aa93-140
			5/14	nt1744-1763	Del and frameshift HBxAg at aa 124-130 with stop codon
			1/14	nt1755-1776	Del and frameshift HBxAg at aa 128-134 with stop codon
		KXY(C)	7/18	nt2848-2862	Del LHBsAg start codon, Del Pol aa181-186
			1/18	nt121	Del and frameshift LHBsAg at aa163 with stop codon, Del and frameshift Pol at aa343 with stop codon
			2/18	nt2197-2212	Del and frameshift PreC/C at aa128-133 with stop codon
			3/18	nt1647	Ins HBxAg aa93-100
			13/18	nt1755-1776	Del and frameshift HBxAg at aa 128-134 with stop codon
			3/18	nt1751-1769	Del and frameshift HBxAg at aa 126-132 with stop codon
		LYL(B)	2/12	nt121	Del and frameshift LHBsAg at aa163 with stop codon, Del and frameshift Pol at aa343 with stop codon
		XDH(C)	1/12	nt2003	Del and frameshift PreC/C at aa64 with stop codon
			2/16	nt2848-2865	Del LHBsAg start codon with stop codon, Del Pol aa181-186
1/16	nt302G-A		Pol W404*		

		LMX(I)	1/16	nt1376G-A	Pol W762*
			1/16	nt1988-2043	Del and frameshift PreC/C at aa59-77 with stop codon
			1/16	nt2081-2241	Del and frameshift PreC/C at aa90-143 with stop codon
			1/16	nt2087-2230	Del PreC/C aa92-139
			9/16	nt2134-2220	Del PreC/C aa108-136