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RESEARCH LETTER

Naturally occurring genotypic drug-resistant mutations of HBV in Huzhou, China: a single-center study

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China is an area with highly endemic hepatitis B virus (HBV) infection, with an estimated 93 million HBV carriers, resulting in approximately 330,000 deaths annually.[1] The predominant HBV genotypes in China are genotype B and C. Currently, nucleos(t)ide analogs are used for anti-HBV treatment. However, prolonged antiviral therapy may lead to drug resistance, which is associated with mutations in the reverse transcriptase region of the HBV genome. Several studies have shown that drug-resistant mutations existed in treatment-naïve patients with chronic hepatitis B (CHB). However, the prevalence rates of natural drug-resistant mutations varied in different reports.[2,3] Furthermore, the prevalence and clinical profile of natural drug-resistant mutations in CHB patients are not quite clear. Thus, the purpose of this study was to investigate the prevalence and clinical feature of natural drug-resistant mutations among treatment-naïve CHB patients in a tertiary hospital in Huzhou, eastern China.

In this study, we recruited 218 CHB patients who had not received anti-HBV treatment in Huzhou Central Hospital. The diagnosis of CHB was done according to the Chinese consensus criteria. This study was approved by the ethics committee of Huzhou Central Hospital in accordance with the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent. Routine serological examination was performed by the technicians in Department of Laboratory Medicine. Serum HBV DNA levels were quantified using real-time polymerase chain reaction. The reverse transcriptase region amplification and sequencing was performed as described previously.[4]

Among 213 successfully sequenced sample from patients, natural drug-resistant mutations were detected in 6.1% (13/213) patients, and these included rtM204I/V (n=8), rtL180M (n=4), rtA181T/V (n=4), rtL80I/V (n=4), rtV173L (n=2), and rtN236T (n=2). The clinical information of these patients is shown in Table 1. The prevalence rates of natural drug-resistant mutations in CHB patients were found to be varied in different areas of China (from 2.01% to 8.9%).[2,3] A meta-analysis revealed that the pooled incidence of natural resistance mutations in China is higher than those in other countries (8.00% vs 1.88%).[5] The incidence rate of natural resistance mutations in our study was not in agreement with the results of other studies. The discordance between previous studies and our results might be due to discrepancy of sample size and differences in study method, genotypic distribution, and study population. The actual prevalence of natural drug-resistant mutations in treatment-naïve patients may

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Table 1 Characteristics of patients with natural drug-resistant mutations

Case No	Sex	Age	HBeAg status	HBV DNA (logIU/mL)	HBV genotype	Drug-resistant mutations
1	M	59	–	4.59	B	A181T N236T
2	F	45	+	6.67	C	V173L L180M M204V
3	M	62	+	4.78	C	V173L
4	M	46	+	4.39	C	A181V
5	M	21	+	7.27	B	L180M M204V
6	M	55	–	4.85	C	L180M M204I
7	M	32	+	7.36	C	V173L M204I
8	F	43	–	6.41	C	A181T N236T
9	M	39	–	3.55	B	L80I M204I
10	M	36	+	6.65	B	L80V M204I
11	F	45	–	7.47	B	L80I M204I
12	F	33	+	4.50	C	L80I L180M M204I
13	M	30	+	8.69	B	A181T

Abbreviation: HBV, hepatitis B virus.

Table 2 Clinical and virological characteristics of patients with and without drug-resistant mutations

Characteristics	Patients with drug-resistant mutations (n=13)	Patients without drug-resistant mutations (n=200)	*P*-value
Gender (male/female)	9/4	141/59	0.570
Age (years)	42.0±11.9	36.2±12.6	0.110
HBeAg status (+/–)	8/5	116/84	0.802
HBV DNA (logIU/mL)	5.93±1.57	6.22±1.71	0.560
HBV genotype(B/C)	6/7	121/76	0.275
ALT (IU/L)	125.1±235.2	152.1±249.3	0.705
AST (IU/L)	100.9±190.8	90.9±165.6	0.834
ALP (IU/L)	103.7±40.9	96.9±39.7	0.549
GGT (IU/L)	79.6±129.4	63.0±85.1	0.511

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus.

be higher than our results show considering the low sensitivity of direct sequencing (mutation frequency >20%). Nonetheless, the current study provides a rationale for the further large-scale investigation on prevalence of natural resistance mutations by the next-generation sequencing technologies.

At present, we compared the clinical and virological characteristics between the patients with and without natural drug-resistant mutations (Table 2). No significant correlation was found between natural drug-resistant mutations and gender, age, HBeAg status, HBV DNA levels, proportion of genotype C, and liver function biochemical markers, including alanine aminotrasferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT) (all $P>0.05$). To date, the clinical significance of natural drug-resistant mutations is unclear. Recently, one study showed that no significant correlation was found between natural drug-resistant mutations and clinical features, including gender, age, genotype, HBeAg status, HBV DNA loads or ALT and AST values.[6] On the contrary, another study reported that natural resistance mutations may be correlated with HBV DNA levels and genotype.[7] Hence, large-scale investigations on natural drug-resistant mutations are needed to further clarify the clinical significance of natural resistance mutations in CHB patients.

In summary, the present study shows that the primary drug-resistance mutations (rtM204V/I, rtA181T/V, and rtN236T) and secondary drug-resistance mutations (rtL80V/I, rtV173L, and rtL180M) existed in treatment-naïve CHB patients in Huzhou, eastern China. Considering that pre-existing drug-resistant mutations may affect the efficiency of antiviral therapy, it is necessary to monitor the nucleos(t)ide analog resistance mutations before antiviral therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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