

Association of rs4646287 Polymorphism with the Risk of Hepatitis B Virus Infection and the Progression of Hepatocellular Carcinoma in an Iranian Population

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ABSTRACT

Background: Hepatitis B virus is responsible for more than one million deaths annually, mainly due to HBV-related diseases and HCC. HBV enters hepatocytes and interacts with the NTCP. While several SNPs have been linked to HBV infection and HCC, further research is needed to clarify the precise role of SNPs. The relationship of the rs4646287 SNP with the risk of HBV infection and the progression of cirrhosis and HCC has been investigated in different populations. This study aimed to evaluate the association of the rs4646287 SNP with HBV infection, cirrhosis, and HCC in an Iranian population.

Methods: The whole blood DNA was extracted from healthy individuals and patients with HBV, cirrhosis, and HCC. Primers for the C and T variants were designed using Primer1. The genotypes of the samples were identified using Tetra-ARMS PCR. The Tetra-ARMS PCR products were analyzed by electrophoresis on 2.5% agarose gels.

Results: Individuals with the rs4646287 TT genotype exhibited a significantly reduced risk of developing cirrhosis and HCC compared to healthy controls. The TT genotype also showed a decreased correlation between the HBV group and those with cirrhosis and HCC.

Conclusion: Our findings suggest that the rs4646287 TT genotype is associated with a lower risk of developing HBV-related diseases and HCC in an Iranian population. **DOI: 10.61186/ibj.4979**

Keywords: Hepatitis B virus, hepatocellular carcinoma, single nucleotide polymorphisms

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INTRODUCTION

Despite the availability of HBV vaccination, HBV remains a major public health problem in low- and middle-income countries. According to the World Health Organization, an estimated 254 million people were infected with this virus in 2024, with around 1.2 million new infections occurring each

year. In 2022, HBV was responsible for 1.1 million deaths, primarily due to cirrhosis or HCC^[1,2].

HBV, cirrhosis, and HCC are closely interconnected. Indeed, most patients diagnosed with HCC have a history of cirrhosis. Research has shown that patients with cirrhosis caused by either HCV or HBV are at high risk of developing HCC^[3,4]. Globally, HBV is recognized as one of the main causes of HCC. HBV

List of Abbreviations:

Bas: bile acid; **CI:** confidence interval; **HBV:** hepatitis B virus; **HCC:** hepatocellular carcinoma; **HCV:** hepatitis C virus; **NTCP:** Sodium taurocholate co-transporting polypeptide; **OR:** Odds ratio; **SNPs:** single nucleotide polymorphism; **Tetra-ARMS PCR:** Tetra-amplification refractory mutation system polymerase chain reaction

Table 4. Association of rs4646287SNP with HBV, cirrhosis, HCC, and their ORs relative to other groups

Groups	p value	OR	p value	95% CI
Control	0.21	-	-	-
HBV	0.69	-	-	-
Cirrhosis	0.09	-	-	-
HCC	0.18	-	-	-
HBV vs. Control	-	1.02	0.86	0.810 - 1.288
Cirrhosis vs. Control	-	0.405	0.00	0.268 - 0.613
HCC vs. Control	-	0.45	0.00	0.311 - 0.667
Cirrhosis vs. HBV	-	0.411	0.00	0.275 - 0.614
HCC vs. HBV	-	0.46	0.00	0.316 - 0.665
HCC vs. Cirrhosis	-	1.08	0.78	0.627 - 1.862

Additionally, the TT rs4646287 SNP genotype seems to reduce the correlation between the HBV, control, and cirrhosis groups in the Iranian population, suggesting the protective role of the TT genotype against cirrhosis and HCC. Our findings regarding the effect of the rs4646287 variant on HBV infection in the Iranian population were consistent with previous studies^[14,23,24]. Research conducted on the Ghanaian population revealed that only rs2296651 was linked to a high risk of HBV infection, while rs4646287 did not show such an association^[15]. Similarly, a study involving a Thai population demonstrated that rs4646287 was not associated with HBV infection or HCC development^[24]. However, an investigation in the Han Chinese population suggested that the rs4646287 SNP variant might be associated with an increased risk of HBV infection. They found that the “CT + TT” genotypes of the rs4646287 SNP were significantly lower in the HCC group compared to the controls^[23].

Cirrhosis is an advanced stage of liver disorder characterized by fibrosis and hepatic parenchymal lesions, often resulting from HBV and HCV infection^[25]. Our findings indicated that HBV-infected patients with the rs4646287 TT genotype had a lower risk of developing cirrhosis and HCC. These results in the Iranian population align with those reported in Han Chinese individuals^[11]. However, our data contrast with some studies conducted in China, where two studies found that the rs4646287 TT genotype is associated with a high risk of HBV-related fibrosis and HCC development^[19,26]. The variations in our findings and those from other studies regarding the association of the rs4646287 SNP with HBV infection, HBV-related diseases, and HCC development suggest that the influence of the rs4646287 SNP might be inconsistent in different populations. These discrepancies could be attributed to differences in sample sizes. Therefore, more studies are necessary to confirm our findings and clarify the relationship between the rs4646287 SNP and HCC development.

CONCLUSION

Our findings suggest that the rs4646287TT SNP may be linked to a lower risk of HBV-related diseases and the development of HCC in the Iranian population. However, further investigations are needed to precisely clarify the role of the rs4646287 SNP in this population.

DECLARATIONS

Acknowledgments

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Ethics approval

This study was approved by the Ethics Committee of Human Research, Publication and Ethics of Shiraz University of Medical Sciences, Shiraz, Iran (ethical code: IR.SUMS.REC.1399.1158).

Consent to participate

All patients voluntarily agreed to participate in this research. Written informed consents were obtained from all participants before they participated in the study.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

HA: designed and directed the investigation, conducted all statistical analyses, and wrote and revised the manuscript; MRF: conducted disease diagnosis and