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Alpha-fetoprotein gene polymorphisms and risk of HCC and cirrhosis

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ABSTRACT

Background: Elevated level of alpha fetoprotein (AFP) is found in approximately 60% of hepatocellular carcinoma (HCC) cases. Other liver diseases including cirrhosis and chronic hepatitis are related with an increased level of AFP. The regulation of *AFP* gene expression has been relatively less studied although the gene has been suggested to play a role in HCC development. This study aimed at identifying genetic variations in *AFP* that might be associated with the presence of HCC and cirrhosis among ethnic Indonesians.
Methods: Direct DNA sequencing was carried out to sequence *AFP* promoter, exons, and 3′ untranslated region (UTR) in DNA samples isolated from 119 HCC, 119 cirrhosis and 105 control subjects. For each sample serum AFP level was determined and association studies with single nucleotide polymorphisms (SNPs) and haplotypes were performed.
Results: In this study we identified 47 SNPs in the *AFP* gene. Statistically significant associations with HCC and cirrhosis were detected for six individual SNPs in the *AFP* promoter, *AFP* intron 1 and intron 2 (rs6834059, rs3796678, rs3796677, rs3796676, rs28532518 and rs4646038). Furthermore, we identified two SNPs in *AFP* intron 7 and 3′UTR, rs2298839 and rs10020432, which are associated with increased risk of cirrhosis.
Conclusion: Genetic variants in the *AFP* gene may be associated with HCC and cirrhosis risk for ethnic Indonesians.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the top 10 most frequent tumor types worldwide with short survival times and few treatment options. Although the disease may take 20–50 years to develop, early detection is not often achieved due to the lack of reliable markers [1]. HCC is a major health-care problem in Asia, where HBV infection is highly endemic. It has been estimated that worldwide 350 million individuals are suffering from chronic HBV infection and as many as 170 million persons are infected with HCV, and thus are at risk of developing cirrhosis and/or HCC [2–4]. Approximately 4.6% of the Indonesian population tested positive for HBV surface antigen (HBsAg), and the estimated HCV prevalence lies between 1 and 2.5% of the Indonesian population [5,6]. Wang et al. surveyed the demographic, clinical and virological characteristics of 414 HCC patients including 107 from China, 15 from India, 101 from Indonesia and 191 from Japan [5]. The most frequent cause for HCC is HBV infection in China, whereas HCV was more common in Japan. The patterns of Indonesia were in between those of China and Japan. The mean age ± SD for HCC patients is 53.7 ± 14.2 years, and male patients predominate with up to 75% of total HCC patients [5].

Alpha fetoprotein (AFP) is a well-recognized tumor marker for HCC; elevated serum AFP concentration is found in approximately 60% of HCC patients [7]. The cutoff concentration of AFP used for diagnosis determines the specificity and sensitivity of AFP as a diagnostic and/or prognostic marker [8]. Variations of serum concentration AFP are observed among HCC patients as well, thus contributing to the complexity in the diagnosis. Various reports have suggested the role of AFP in the cell as a superoxide dismutase [9] and as an apoptotic

Abbreviations: AFP, Alpha fetoprotein; HCC, Hepatocellular carcinoma; SNP, Single nucleotide polymorphism; HBV, Hepatitis B virus; HCV, Hepatitis C virus; UTR, Untranslated region; LD, Linkage disequilibrium; OR, Odds ratio; CI, Confidence interval; PCR, Polymerase chain reaction.

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