MDM2 Promoter SNP309 Is Associated with the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C

Narayan Dharel, Naoya Kato, Ryosuke Muroyama, Masaru Moriyama, Run-Xuan Shao, Takao Kawabe, and Masao Omata

Abstract

Purpose: A single nucleotide polymorphism (SNP) in the promoter region of MDM2 gene, SNP309, has recently been shown to be associated with accelerated tumor formation in both hereditary and sporadic cancers in humans. However, the association of SNP309 with hepatocellular carcinoma is unknown. We evaluated the association of SNP309 with the risk of hepatocellular carcinoma development among Japanese patients with chronic hepatitis C virus infection.

Experimental Design: We genotyped the SNP309 at the MDM2 promoter in 435 Japanese patients with chronic hepatitis C virus infection, including 187 patients with hepatocellular carcinoma and 48 healthy subjects, using a fluorogenic PCR. Presence of SNP was also confirmed by direct sequencing of the MDM2 promoter region.

Results: The proportion of G/G genotype of the SNP309 in patients with hepatocellular carcinoma (33%) was significantly higher than that in patients without hepatocellular carcinoma (23%), with an odds ratio (95% confidence interval) of 2.28 (1.30-3.98). A multivariate analysis revealed that MDM2 SNP309 (G/G versus T/T), age >60 years, male gender, presence of cirrhosis, serum α-fetoprotein >20 μg/L, and serum albumin <3.2 g/dL were independently associated with the hepatocellular carcinoma development at odds ratio of 2.27, 2.46, 3.08, 4.15, 4.87, and 6.33, respectively.

Conclusions: The MDM2 promoter SNP309 is associated with the presence of hepatocellular carcinoma in Japanese patients with chronic hepatitis C.

It has been estimated that hepatitis C virus (HCV) infects at least 170 million people worldwide, which often leads to the dreadful sequels of cirrhosis, end-stage liver disease, and hepatocellular carcinoma (1–4). The risk of hepatocellular carcinoma development increases with the severity of inflammation and liver fibrosis (5–7). Several factors, such as alcohol intake, older age at time of infection, male gender, and coinfection with the hepatitis B virus or HIV, are known to accelerate disease progression in HCV infection (5, 7, 8). In addition, host genetic factors have been reported to affect the outcome of HCV infection (9–15).

Recently, we reported that genetic polymorphisms in interleukin-1β and UDP glucuronosyltransferase 1A7 genes were associated with the development of hepatocellular carcinoma in Japanese patients with chronic HCV infection (13, 14), which was followed by similar reports by other groups as well (16). We further did a large-scale search of gene polymorphisms associated with the hepatocellular carcinoma development in a much larger population of HCV patients and found that three single nucleotide polymorphisms (SNP) in three genes (SCYB14, GFRA1, and CRHR2) were significantly associated with hepatocellular carcinoma development in Japanese patients with chronic HCV infection (15).

The association of both the germ-line and somatic inactivating mutations of the p53 gene with increased tumor development is well known (17–20). Gene polymorphisms at critical nodes of the p53 pathways have also been reported to be associated with development of cancers (21–23). Recently, a SNP (SNP309, rs2279744) in the promoter region of MDM2, a negative regulator of p53, has been shown to be associated with accelerated tumor formation in both hereditary and sporadic cancers in humans (24). However, it is not known whether the SNP309 is associated with the development of hepatocellular carcinoma as well.

In the present study, we investigated the association of the MDM2 promoter SNP309 with development of hepatocellular carcinoma among Japanese patients with chronic HCV infection.

1 http://www.who.int/inf-fs/en/fact64.html.
Patients and Methods

Patients. We studied 435 consecutive Japanese patients with chronic HCV infection who consulted the outpatient clinic of the University of Tokyo Hospital between August 2001 and June 2003 (239 men and 196 women; ages 22-84 years; median, age 62 years; 187 with hepatocellular carcinoma and 248 without hepatocellular carcinoma). To obtain an estimate of the genetic distribution of the SNP309 in the general Japanese population, we also obtained DNA samples from 48 healthy individuals who visited our hospital (41 men and 7 women; ages 23-53 years; median age, 34 years) with no history of liver diseases. The genomic DNA of these patients was made available after obtaining written informed consent for genotyping. Approval was obtained from the institutional ethics committee, and all the procedures followed institutional guidelines (25). Patients selected for the study were those who tested positive for HCV antibody by the second-generation enzyme immunoassay (Ortho Diagnostics, Tokyo, Japan), and HCV RNA was measured using the Amplicor HCV assay version 1 (Roche, Tokyo, Japan). All patients were negative for the hepatitis B surface antigen (Abbott Laboratories, North Chicago, IL). HCV genotypes were determined using a genotyping assay (SRL Laboratory Co., Tokyo, Japan). Any patients with an ethanol intake of >80 g/d for >10 years were considered to have a positive history of alcohol abuse. The following clinical variables were obtained for each patient at the time of whole-blood collection: age, gender, serum albumin level, serum total bilirubin level, serum alanine aminotransferase level, serum alpha-fetoprotein (AFP) level, prothrombin time, platelet count, and serum viral load measured using the Amplicor HCV monitor assay. The diagnosis of hepatocellular carcinoma was made by several imaging methods (ultrasonography, computed tomography, arteriography, or magnetic resonance imaging) and confirmed histologically by sonography-guided fine-needle biopsy in all 187 patients. All patients were shown not to have other cancers by an initial screening examination.

SNP genotyping. Genomic DNA was extracted from 100 µL whole blood using the SepaGene kit (Sanko Junyaku, Tokyo, Japan) according to the manufacturer’s instructions. Extracted DNA was dissolved in 20 µL Tris-HCl buffer (10 mM, pH 8.0) containing 1 mM EDTA and was stored at −30°C until use.

We did the SNP genotyping using the Taqman SNP genotyping assays and ABI 7000 sequence detection system (Applied Biosystems, Foster City, CA). The PCR contained genomic DNA (10 ng), 1 µL Taqman universal PCR master mix, forward and reverse primers (900 nM each), MGB probes, and 200 ng/mL of FAM-labeled probe. The genotyping was done using the Custom Taqman SNP genotyping Assay protocol (Applied Biosystems) and were as follows: forward primer 5’-CGGGAGTTCA-GGTTAAGGT-3’ and reverse primer 5’-ACAGGCCACCTGGCATCCT-3’, VIC-labeled probe 5’-TCTCCCCCGCCGAAG-3’, and FAM-labeled probe 5’-TCCGGGCGCGCAG-3’. The probes were MGB probes designed specifically for Taqman Allelic Discrimination (Applied Biosystems). The PCR was carried out in 96-well plate with a reaction volume of 25 µL. Each 96-well plate contained 88 samples of unknown genotype, two samples of each of the T/T, T/G, and G/G genotypes as positive control and two no-template controls. Thermal cycle conditions were 50°C for 2 minutes, 95°C for 10 minutes, and 40 cycles of 92°C for 15 seconds and 60°C for 1 minute. Complete PCR plates were read on an ABI PRISM 7000 sequence detector and analyzed using the Allelic Discrimination Sequence Detection Software (Applied Biosystems).

As confirmatory check of the SNP genotyping, a short segment of intron 1 of the MDM2 gene of randomly selected samples was amplified by PCR using the following primers: 5’-CGGGAGTTCA-GGTTAAGGT-3’ and 5’-AGCAAGTCGGTGCTTACCTG-3’ (24) and was checked by direct sequencing. Because the results of allelic discrimination were 100% concordant with the direct sequencing, the rest of the genotyping was done using the Taqman systems only.

Results

Patient characteristics. The characteristics of the total 435 patients with chronic HCV infection involved in the study are shown in Table 1. There were no significant differences in the HCV serotype, viral load, serum alanine aminotransferase levels, and alcohol use between the group of patients with and without hepatocellular carcinoma. In patients with hepatocellular carcinoma, however, age, proportion of male gender, presence of cirrhosis, serum total bilirubin, and serum AFP levels were higher and serum albumin levels, prothrombin time, and platelet counts were lower than in patients without hepatocellular carcinoma.

MDM2 promoter SNP309 polymorphisms in HCV-infected patients and healthy subjects. We examined the SNP309, located in the promoter region (intron 1) of the MDM2 gene, in all 483 subjects (435 patients and 48 healthy individuals) using the Taqman SNP genotyping method. The presence of SNP was also confirmed by direct sequencing of randomly selected samples. The distributions of the SNP309 genotypes, alleles, and at-risk alleles with regard to the presence or absence of hepatocellular carcinoma are shown in Table 2. Data from the 48 healthy subjects are also shown for comparison. There was no difference in the distribution pattern of the SNP309 (T/T, T/G, and G/G genotypes) among healthy individuals and patients with chronic HCV infection. However, when the HCV patients were segregated into two groups based on presence or absence of hepatocellular carcinoma, the genotype frequencies and allelic frequencies of SNP309 were significantly different between the groups of patients with and without hepatocellular carcinoma. The at-risk alleles were also associated with the presence of hepatocellular carcinoma. For instance, the frequency of distribution of T/T versus G/G genotype among those who had developed hepatocellular carcinoma (16% versus 33%) was significantly different from those who had not developed hepatocellular carcinoma (27% versus 23%; P = 0.004). In other words, a higher number of patients with hepatocellular carcinoma were found to have the G/G genotype compared with the patients without...
hepatocellular carcinoma, whereas the T/T genotype was more common among the nonhepatocellular carcinoma group than the hepatocellular carcinoma group.

The proportion of G/G genotypes of the MDM2 SNP309 among patients with hepatocellular carcinoma (33%) was higher than in patients without hepatocellular carcinoma (23%) and the healthy subjects (27%). Of the T/T, T/G, and G/G genotypes, 32%, 43%, and 52% had hepatocellular carcinoma, respectively. Having a G allele gradually increased the proportion of patients with hepatocellular carcinoma ($P = 0.0135$). The MDM2 SNP309 genotype T/G and G/G as opposed to genotype T/T increased the risk of hepatocellular carcinoma with the OR (95% CI) of 1.62 (0.98-2.68; $P = 0.057$) and 2.28 (1.30-3.98; $P = 0.004$), respectively. The attributable risks of MDM2 SNP genotype T/G to T/T and G/G to T/T were 11% and 20%, respectively.

We also checked the effect of SNP309 on the rate of fibrosis progression and presence of cirrhosis; however, there were no significant difference among the three genotypes of SNP309 with regard to these variables.

Factors associated with presence of hepatocellular carcinoma in HCV-infected patients. The following factors were significantly associated with the presence of hepatocellular carcinoma according to univariate analyses: MDM2 SNP309 ($P = 0.0137$), age >60 years ($P < 0.0001$), male gender ($P = 0.001$), presence of cirrhosis ($P < 0.0001$), serum albumin <3.2 g/dL ($P < 0.0001$), total bilirubin >0.7 mg/dL ($P < 0.0001$), AFP >20 µg/L ($P < 0.0001$), prothrombin time <70% ($P < 0.0001$), and platelet count <12.5 x 10^4/µL ($P < 0.0001$). To evaluate the effect of MDM2 SNP309 polymorphisms on the presence of hepatocellular carcinoma, a multivariate logistic regression analysis was done with these nine variables. Six variables (SNP309 genotypes, presence of cirrhosis, age >60 years, male gender, and serum AFP >20 µg/L and serum albumin <3.2 g/dL) were included in the final model with OR (95% CI) of 2.27 (1.11-4.70; T/T versus G/G), 4.15 (2.46-7.08), 2.46 (1.42-4.31), 2.46 (1.42-4.31),

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Total (n = 435)</th>
<th>Without hepatocellular carcinoma (n = 248)</th>
<th>With hepatocellular carcinoma (n = 187)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>247 (57)</td>
<td>128 (52)</td>
<td>119 (64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (22-84)</td>
<td>59 (22-80)</td>
<td>65 (38-84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>189 (43)</td>
<td>56 (23)</td>
<td>133 (71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCV serotype 1</td>
<td>285 (77)</td>
<td>158 (77)</td>
<td>127 (77)</td>
<td>0.993</td>
</tr>
<tr>
<td>HCV load (IU/mL)</td>
<td>434 (0.5-1910)</td>
<td>435 (0.5-1910)</td>
<td>430 (0.5-1340)</td>
<td>0.514</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9 (2.3-5.0)</td>
<td>4.1 (2.3-5.0)</td>
<td>3.6 (2.3-4.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.8 (0.2-6.7)</td>
<td>0.7 (0.2-6.7)</td>
<td>0.9 (0.3-3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alanine aminotransferase (units/L)</td>
<td>60 (14-465)</td>
<td>55 (14-433)</td>
<td>65 (15-465)</td>
<td>0.142</td>
</tr>
<tr>
<td>AFP (µg/L)</td>
<td>11.5 (1.0-6107)</td>
<td>6 (1.0-425)</td>
<td>35 (3-6107)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>77 (7.3-100)</td>
<td>84 (7.3-100)</td>
<td>72 (13-100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelet count (×10^4/µL)</td>
<td>12.7 (1.7-39)</td>
<td>15 (2.6-34)</td>
<td>9.6 (1.7-39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol (&gt;80 g/d)</td>
<td>15 (3)</td>
<td>7 (3)</td>
<td>8 (4)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

*Age, albumin, total bilirubin, alanine aminotransferase, AFP, prothrombin time, platelet count, and HCV load are shown as median (range). Male, cirrhosis, alcohol, and HCV serotype 1 are shown as frequency (%).

Calculated using the $χ^2$ test.

Calculated using the Wilcoxon test.

### Table 2. SNP309 genotype frequencies in patients with HCV and healthy subjects

<table>
<thead>
<tr>
<th>SNP309</th>
<th>Total (n = 435)</th>
<th>Nonhepatocellular carcinoma (n = 248)</th>
<th>Hepatocellular carcinoma (n = 187)</th>
<th>OR (95% CI) hepatocellular versus nonhepatocellular carcinoma</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>97 (22)</td>
<td>66 (27)</td>
<td>31 (16)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>T/G</td>
<td>220 (51)</td>
<td>125 (50)</td>
<td>95 (51)</td>
<td>1.62 (0.98-2.68)</td>
<td>0.057</td>
</tr>
<tr>
<td>G/G</td>
<td>118 (27)</td>
<td>57 (23)</td>
<td>61 (33)</td>
<td>2.28 (1.30-3.98)</td>
<td>0.004</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>414 (48)</td>
<td>257 (52)</td>
<td>157 (42)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>456 (52)</td>
<td>239 (48)</td>
<td>217 (58)</td>
<td>1.49 (1.13-1.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>At-risk allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/G + T/T</td>
<td>317 (73)</td>
<td>191 (77)</td>
<td>126 (67)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>118 (27)</td>
<td>57 (23)</td>
<td>61 (33)</td>
<td>1.62 (1.06-2.48)</td>
<td>0.025</td>
</tr>
<tr>
<td>T/G</td>
<td>97 (22)</td>
<td>66 (27)</td>
<td>31 (16)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>G/G + T/G</td>
<td>338 (78)</td>
<td>182 (77)</td>
<td>156 (84)</td>
<td>1.83 (1.13-2.94)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*Values expressed as n(%).
Our results showed an effect of the SNP309 genotypes and the outcome of chronic HCV infection. Our results showed that the G/G genotype of the SNP309 has a strong effect on tumorigenesis on humans (24). We studied the effect of the SNP309 on hepatocellular carcinoma development in HCV-infected patients. A prospective controlled study can be done to evaluate this phenomenon in future.

The SNP309 lies in the Sp1-binding site in the promoter region of MDM2 gene. A T-to-G substitution in this region increases the binding affinity of the transcriptional activator Sp1, which results in high levels of MDM2 RNA and protein (24, 29). The heightened MDM2 levels are poor prognostic factors in many human cancers, including lung cancers and breast cancers (30, 31). MDM2 is a key negative regulator of p53, the most important tumor suppressor (32, 33), which targets p53 for proteosomal degradation (33–35). A high MDM2 level (as is seen in the SNP309 G/G genotype) leads to the attenuation of the p53 DNA damage response that allows increased cell proliferation and inhibition of apoptosis, providing advantageous signals for tumor cell survival (29, 34, 36).

Studies using MDM2 transgenic mice have shown that 100% of the MDM2-overexpressing mice developed spontaneous tumors in a lifetime (37). These studies, together with numerous accounts of MDM2 overexpression or amplification in a variety of human cancers, support the idea that heightened levels of MDM2, as seen in SNP309 G/G genotype, could positively affect tumor formation.

In Japan, >80% of hepatocellular carcinoma are caused by the HCV infection alone (3, 38, 39). Persistent of the viral infection in hepatic cells is strongly associated with the hepatocellular carcinoma development (2, 5, 6). In a recent report, Arva et al. showed that the SNP309 G allele results into MDM2-p53 complex that is transcriptionally inactive (36). In a related but different study, we have found that although a strong p53 expression suppresses replication of the HCV in vitro, the viral replication is significantly enhanced when p53 gene expression is suppressed.3 Inactivating gene mutations of p53 are common in patients with hepatocellular carcinoma (40, 41) but are not as frequent as in other malignancies, such as ovarian, esophageal, or colon cancers (42). A high prevalence of G alleles of the SNP309 in the hepatocellular carcinoma patients, on the other hand, implies that the p53 functions in the HCV patients could have been indirectly suppressed by the heightened MDM2 levels, making them more vulnerable to cancer development. Together, these data support a model whereby SNP309 enhances the affinity of the transcriptional activator Sp1 to the promoter of the MDM2 gene, resulting in heightened transcription. Heightened levels of MDM2 lead to the direct inhibition of p53 transcriptional activity, which, in patients with chronic hepatitis C, could lead to an unrestricted replication and proliferation of the HCV inside hepatic cells, ultimately leading to tumor development. It has been suggested that the G allele can serve as a rate-limiting event in the formation of a tumors in humans based on the Knudson model (29, 43). Based on our results, we can assume a codominant model (i.e., one G allele increases the risk of having hepatocellular carcinoma and two G alleles further increase the risk).

Despite the limitations of a cross-sectional study, our analysis showed a prominent effect of the SNP309 G/G genotype on the risk of developing hepatocellular carcinoma. Most HCV-related hepatocellular carcinomas arise from a background of cirrhosis, to an accelerated hepatocellular carcinoma development in HCV-infected patients.

Table 3. Factors associated with presence of hepatocellular carcinoma in HCV-infected patients in multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP309</td>
<td>T/T</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T/G</td>
<td>1.53 (0.81-2.93)</td>
<td>0.192</td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>2.27 (1.11-4.70)</td>
<td>0.025</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Presence</td>
<td>4.15 (2.46-7.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60 y</td>
<td>2.46 (1.42-4.31)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>3.08 (1.80-5.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AFP</td>
<td>&gt;20 µg/L</td>
<td>4.87 (2.87-8.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;3.2 g/dL</td>
<td>6.33 (1.91-29.4)</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

Discussion

In this study, we identified a potential genetic marker for susceptibility to hepatocarcinogenesis in patients with chronic HCV infection. We evaluated the relationships between the MDM2 SNP309 genotypes and the outcome of chronic HCV infection. Our results showed an effect of the MDM2 SNP309 polymorphisms on the presence of hepatocellular carcinoma after controlling for other confounding clinical variables. The proportion of patients with hepatocellular carcinoma gradually increased from the SNP309 genotype of T/T to T/G to G/G. The SNP309 allele G was found to be associated with the presence of hepatocellular carcinoma. Our multivariate model confirmed the association between the SNP309 G/G genotype and the presence of hepatocellular carcinoma. Further, our results showed that the genotype frequencies in patients with cirrhosis but without hepatocellular carcinoma were similar to those in patients without cirrhosis and hepatocellular carcinoma, suggesting that this polymorphism is not as strongly associated with the presence of cirrhosis.

The MDM2 SNP309 was recently identified by Bond et al., who, using samples of breast cancers and soft-tissue sarcomas, showed that the G/G genotype of the SNP309 has a strong effect on tumorigenesis on humans (24). We studied the effect of the SNP309 on hepatocellular carcinoma development in patients with chronic hepatitis C and found that G/G genotype is significantly associated with hepatocellular carcinoma. The frequency of SNP309 in our study population of Japanese patients (27%) was higher than in the Caucasians (12%) as was originally reported by Bond et al. (24). Reports from Chinese populations also show a higher frequency of the G/G genotypes, much closer to our findings (27). This may be due to a racial difference of the study population. Using 88 patients of hereditary cancer (Li-Fraumeni syndrome) and 105 sporadic soft-tissue sarcomas, Bond et al. also showed that SNP309 associates with at least 9 years earlier onset of tumors in both hereditary and sporadic cancers (24). Similar findings have been recently reported by at least one other group (28). We also studied the effect of SNP309 on the age of onset of hepatocellular carcinoma; however, we did not find a significant age difference between T/T and G/G genotypes. Owing to the limitations of a cross-sectional design, our present study is unable to comment on whether SNP309 actually leads

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3Unpublished data.
but it is noteworthy that the association of the SNP309 and hepatocellular carcinoma was completely independent of the presence of cirrhosis. Given that many patients are referred to our hospital for the treatment of hepatocellular carcinoma, our study population may be biased toward patients with hepatocellular carcinoma. Our multivariate model, however, included most of the previously reported risk factors for hepatocellular carcinoma (i.e., age, male gender, presence of cirrhosis, AFP level, and serum albumin; refs. 13–15, 44, 45) as well as the polymorphisms of the SNP309. This implies that our results can be generalized to the Japanese population. The uncertainty of the ORs, owing to the study design, should be resolved in subsequent prospective controlled studies. In conclusion, MDM2 promoter SNP309 is associated with the risk of hepatocellular carcinoma among Japanese patients with chronic HCV infection. The G allele of MDM2 SNP309 could serve as an important marker to identify the subgroup of chronic HCV patients at a higher risk of hepatocellular carcinoma.

References

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