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*Review Article*

# Association between *MDM2* rs2279744 and hepatocellular carcinoma risk: results of a meta-analysis

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**Abstract:** Previous studies have investigated the association between *MDM2* rs2279744 and Hepatocellular carcinoma (HCC) susceptibility in both Asian and Caucasian, however, results between them were inconsistent. Therefore, we performed a meta-analysis to try to get a definite evaluation of the association A systematic search of relevant studies on the association was conducted in databases. Odds ratios (ORs) and 95% confidence intervals (CIs) under the allelic model, dominant model, recessive model, and homozygous model were used to evaluate the pooled effect size. Our results suggested that *MDM2* rs2279744 GG was significantly associated with higher occurrence of HCC (Overall, GG vs. GT+TT: OR = 1.55; 95% CI = 1.31-1.85; *P* = 0.000) as well as hepatitis-related HCC (GG vs. GT+TT: OR = 1.26; 95% CI = 1.11-1.44; *P* = 0.001) compared with non-HCC controls, especially in the recessive model. Besides, significant association was also shown between *MDM2* rs2279744 and hepatitis susceptibility in recessive model (GG vs. GT+TT: OR = 1.18; 95% CI = 1.03-1.36; *P* = 0.020). These results indicated that *MDM2* rs2279744 GG could potentially be used to predict the development of HCC, though these findings must be confirmed in well designed subsequently researches.

**Keywords:** *MDM2*, rs2279744, hepatocellular carcinoma, SNP

## Introduction

HCC is the common malignant neoplasm in the world and is estimated to cause more than 600,000 deaths each year [1]. Several oncogenic factors are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcoholism, aflatoxin intake and heredity factors [2]. Patients with chronic HBV infection are at a higher risk of developing hepatic sclerosis and even HCC during their lifetime. However, only 2-10% of HBV-infected individuals occur chronic complications, and the clinical outcomes are vary [3, 4], which drives us to investigate the potential pathogenesis of HCC for chronic HBV or HCV patients.

The epidemiology of HCC is characterized by marked differences between geographical areas, genders, and ethnic groups [5]. Single nucleotide polymorphisms (SNP) in the genes that involved in the inflammatory, tumor angiogenesis, apoptosis, carcinogen metabolism and DNA repair may be associated with differences of tumorigenesis, such as *IL-23R* and *LEP* polymorphisms in Egyptian patients [6], *EGF* polymorphisms in the Chinese Han population [7], genetic variants in *IL-6* and *IL-10* in chronic HCV Tunisian patients [8], *GSTT1, HYL1*2* and *XRCC1* polymorphisms in a population of Gambia [9], and *Fas* and *FasL* gene polymorphisms in Korean [10].

The mouse double minute 2 (*MDM2*), a gene located on chromosome 12q13-14, encodes a nuclear-localized E3 ubiquitin ligase which can promote tumor formation by targeting tumor suppressor proteins, such as p53. Previous studies have investigated the association between *MDM2* polymorphisms and HCC suscep-

**Table 1.** Main characteristics and genotype frequencies in cases and controls of included studies

| Author (year) | Ethnicity | Genotype method | Cases/Controls | Cases | | | Controls | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | TT | TG | GG | TT | TG | GG |
| Akkiz 2010 | Non-Asian | PCR-RFLP | 110/110 | 25 | 56 | 29 | 47 | 48 | 15 |
| Ezzikouri 2009 | Non-Asian | PCR-RFLP | 96/222 | 39 | 46 | 11 | 120 | 89 | 13 |
| Vuolo 2011 | Non-Asian | PCR-RFLP | 61/122 | 13 | 32 | 16 | 55 | 48 | 19 |
| Su 2011 | Asian | MALDI-TOF | 160/160 | 23 | 80 | 57 | 49 | 71 | 40 |
| Tian 2016 | Asian | PCR-RFLP | 101/102 | 19 | 25 | 57 | 20 | 36 | 46 |
| Leu 2009 | Asian | PCR-RFLP | 58/138 | 11 | 37 | 10 | 35 | 80 | 23 |
| Tomoda 2012 | Asian | MALDI-TOF | 258/199 | 41 | 129 | 88 | 47 | 96 | 56 |
| Wang 2012 | Asian | PCR-RFLP | 310/794 | 29 | 116 | 165 | 113 | 345 | 336 |
| Dharel 2006 | Asian | TaqMan assay | 187/296 | 31 | 95 | 61 | 75 | 151 | 70 |
| Yang 2013 | Asian | TaqMan assay | 350/326 | 89 | 176 | 85 | 78 | 166 | 82 |
| Yoon 2008 | Asian | PCR-RFLP | 287/296 | 45 | 125 | 117 | 83 | 132 | 81 |
| Wang 2014 | Asian | PCR-RFLP | 166/157 | 35 | 94 | 37 | 49 | 87 | 21 |
| Qiu 2015 | Asian | PCR-RFLP | 985/992 | 213 | 492 | 280 | 239 | 493 | 260 |
| Li 2013 | Asian | TaqMan assay | 192/192 | 59 | 59 | 80 | 119 | 38 | 35 |

tibility in both Asian and non-Asian, however, results between them were inconsistent. Some studies have demonstrated that *MDM2* rs2279744 is associated with increased risk of HCC in Turkish, Japanese, Italian and several Chinese population of specific region [11-18]. In contrast, there is no significant association was found between *MDM2* rs2279744 and HCC susceptibility in some East Asian population and a Moroccan population [19-24].

In consideration of inconclusive results, the objective of the present study was to assess systematically the association between *MDM2* rs2279744 and HCC susceptibility based on previously published studies in English and Chinese.

## Materials and methods

### *Literature search*

Case-control studies that contain the association of *MDM2* rs2279744 and HCC were identified by an extensive literature search in PubMed, Google Scholar, and Chinese National Knowledge Infrastructure (CNKI) databases up to August 1, 2017. Articles were sought with the following key words and MeSH terms without any language restriction: "mouse double minute 2 or *MDM2*" and "Hepatocellular carcinoma or HCC" and "rs2279744 or SNP309 polymorphism".

### *Inclusion criteria*

Candidate studies had to satisfy the following criteria: (1) a case-control study that committed to investigate the association between *MDM2* rs2279744 and HCC risk; (2) had exact number of allele and genotype frequencies in case and control group for estimating OR (95% CI); (3) there was no other types of tumor cells in control population.

### *Data extraction*

Information including first author's name, year of publication, ethnicity, genotyping methods, sample size, and allele and genotype frequencies in cases and controls were collected by two of the authors independently and reached an agreement on all items.

### *Statistical analysis*

To investigate the association between *MDM2* rs2279744 and HCC susceptibility, the allelic model, genetic models (dominant model analysis and recessive model analysis), and homozygous model were examined. Subgroup analysis based on ethnicity was also performed. The strength of the association between *MDM2* rs2279744 and HCC risk were measured by pooled ORs and 95% CIs. The statistical heterogeneity among included studies was assessed using the *Q*-statistic test and $I^2$ test [25, 26]. The fixed-effect model was used when the *P*

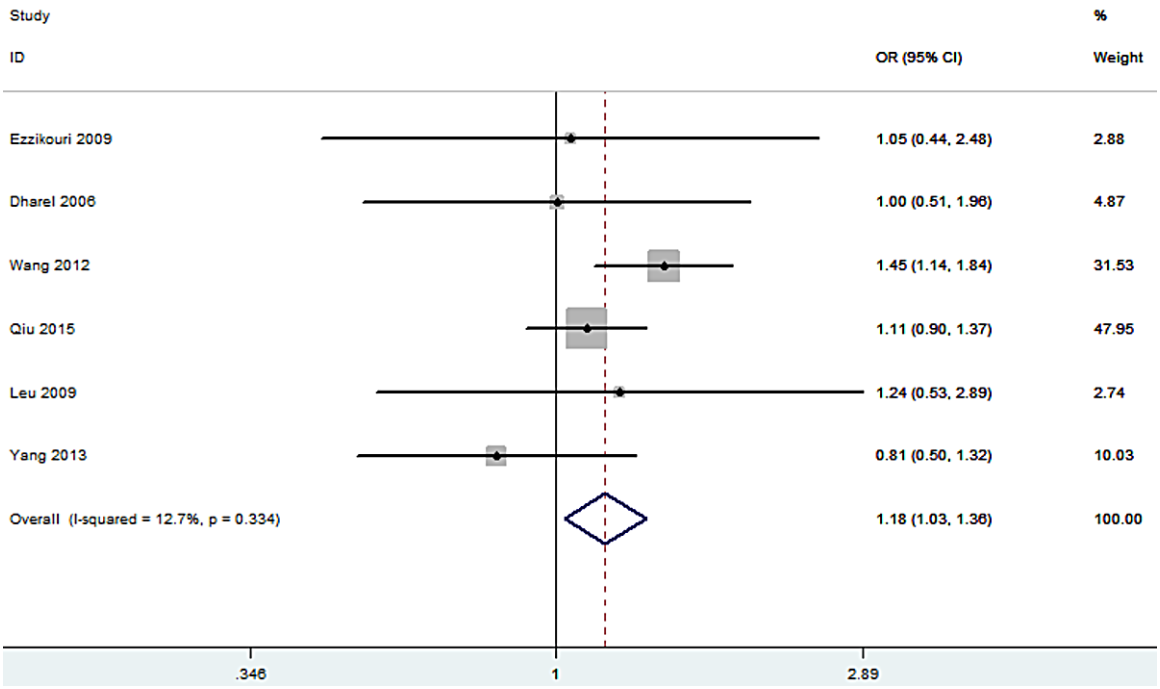


**Figure 1.** Forest plot for GG vs. GT+TT of the association between rs2279744 and hepatitis susceptibility.

**Table 2.** Meta-analysis for the association between rs2279744 and susceptibility to HCC

| Comparison model | Ethnicity | Test of heterogeneity | | Effect model | Test of association | |
|---|---|---|---|---|---|---|
| | | $I^2$ | $P^a$ | | OR (95% CI) | $P^b$ |
| G vs. T | Non-Asian | 0.00% | 0.604 | Random | 1.81 (1.45-2.28) | 0.000 |
| | Asian | 83.10% | 0.000 | Random | 1.44 (1.20-1.73) | 0.000 |
| | Overall | 80.50% | 0.000 | Random | 1.51 (1.28-1.77) | 0.000 |
| GG vs. TT | Non-Asian | 0.00% | 0.835 | Random | 3.26 (1.99-5.32) | 0.000 |
| | Asian | 74.90% | 0.000 | Random | 1.92 (1.41-2.60) | 0.000 |
| | Overall | 71.90% | 0.000 | Random | 2.09 (1.58-2.76) | 0.000 |
| GG+GT vs. TT | Non-Asian | 0.20% | 0.367 | Random | 2.21 (1.59-3.08) | 0.000 |
| | Asian | 75.60% | 0.000 | Random | 1.51 (1.34-1.71) | 0.000 |
| | Overall | 72.60% | 0.000 | Random | 1.58 (1.41-1.77) | 0.000 |
| GG vs. GT+TT | Non-Asian | 0.00% | 0.952 | Random | 2.10 (1.36-3.24) | 0.001 |
| | Asian | 60.90% | 0.004 | Random | 1.50 (1.24-1.81) | 0.000 |
| | Overall | 54.80% | 0.007 | Random | 1.55 (1.31-1.85) | 0.000 |

[a]*P* value for heterogeneity based on Q test. [b]*P* value for association calculated by the Z test.

value more than 0.10 for the *Q*-statistic test and $I^2$ less than 50% which were considered less heterogeneity among included studies; otherwise, the random-effect model was applied. Publication bias was assessed by a Begg's funnel plot and an Egger's linear regression test. *P* value of the Egger's test less than 0.05 was considered significant publication bias. STATA statistical software package (version 11.0; Stata Corporation, College Station, TX) was used to analyze all statistical analysis.

## Results

### *Characteristics of included studies*

After literature search following the mentioned key words, a total of 191 potentially relevant

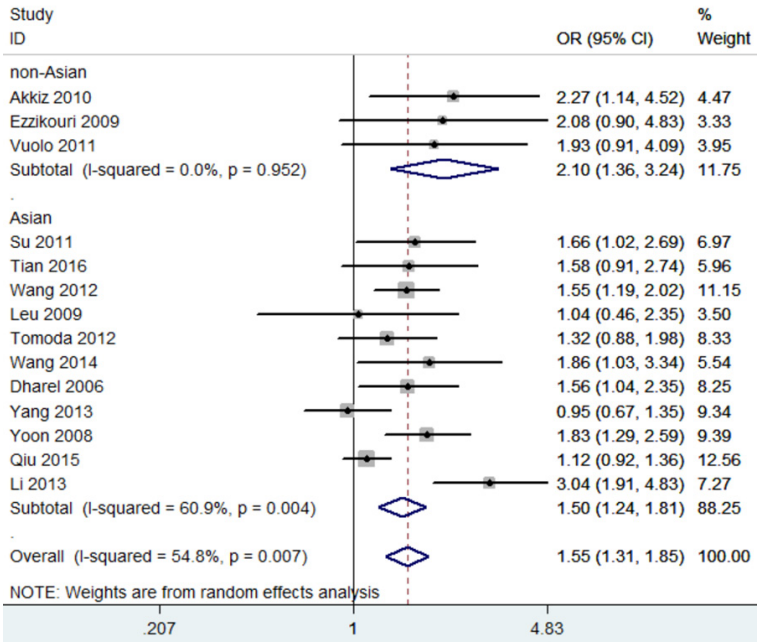


**Figure 2.** Forest plot for GG vs. GT+TT of the association between rs2279744 and HCC susceptibility under subgroup analysis base on ethnicity.

articles were identified. Based on title and abstract, 177 articles were considered not eligible for inclusion. Finally, 14 relevant studies including 11 Asians [13-19, 21-24] and 3 non-Asians [11, 12, 20], which provided 3321 HCC cases and 4106 controls were included in this meta-analysis after reading the text carefully. Main characteristics and genotype frequencies in cases and controls of included studies were summarized in **Table 1**. A review of data extraction revealed 100% agreement between the 2 reviewers.

*MDM2 rs2279744 in hepatitis patients and healthy controls*

Six of the included studies recorded sample size and distribution of genotype frequencies in both HBV and HCV infected individuals and healthy controls. After pooled-analyzing these studies, significant association was shown between *MDM2* rs2279744 and hepatitis susceptibility in recessive model (GG vs. GT+TT: OR = 1.18; 95% CI = 1.03-1.36; *P* = 0.020) (**Figure 1**), which demonstrated that rs2279744 "GG" is an increased risk factor of hepatitis in comparison with "GT+TT". However, no statistically significant association was found in other three models.

*MDM2 rs2279744 in HCC patients and non-HCC controls*

All the included studies have investigated the correlation of *MDM2* rs2279744 and HCC risk although results were inconsistent. Random effect was applied in all comparison models, namely allele model, dominant model, recessive model and homozygous model. In these models, rs2279744 is associated with an increased HCC risk both in the overall and subgroup analysis base on ethnicity (**Table 2**), especially in recessive model (Overall: OR = 1.55; 95% CI = 1.31-1.85; *P* = 0.000; non-Asian: OR = 2.10; 95% CI = 1.36-3.24; *P* = 0.001; Asian: OR = 1.50; 95% CI = 1.24-1.81; *P* = 0.000) (**Figure 2**).

*MDM2 rs2279744 in hepatitis-related HCC patients and non-HCC controls*

Significant differences of *MDM2* rs2279744 were found between hepatitis-related HCC patients and non-HCC controls. And significant trend for the association between *MDM2* rs2279744 and hepatitis-related HCC susceptibility was found in all the comparison models (G vs. T: OR = 1.27; 95% CI = 1.09-1.48; *P* = 0.002; GG vs. TT: OR = 1.57; 95% CI = 1.16-2.11; *P* = 0.003; GG+GT vs. TT: OR = 1.43; 95% CI = 1.12-1.82; *P* = 0.004; GG vs. GT+TT: OR = 1.26; 95% CI = 1.11-1.44; *P* = 0.001), which demonstrated that rs2279744 could increase the risk of developing HCC in hepatitis patients (**Figure 3**).

*Assessment of publication bias*

Publication bias of the included studies was assessed by a Begg's funnel plot and an Egger's linear regression test. The sharp of the Begg's funnel plot appeared to not obvious asymmetry (**Figure 4**). And results of the Egger's linear regression test in accordance with the sharp of the Begg's funnel plot which did not show any statistical evidence of publication bias under the four models with a value of *P* > 0.05.

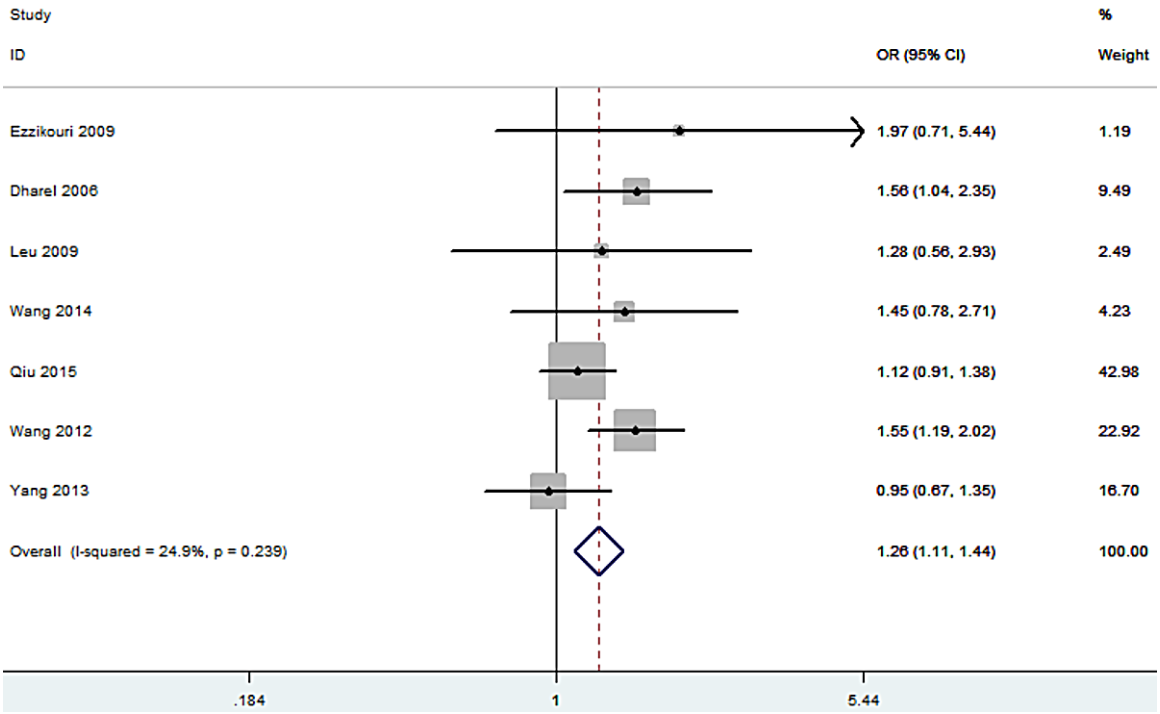


**Figure 3.** Forest plot for GG vs. GT+TT of the association between rs2279744 and hepatitis-related HCC susceptibility.

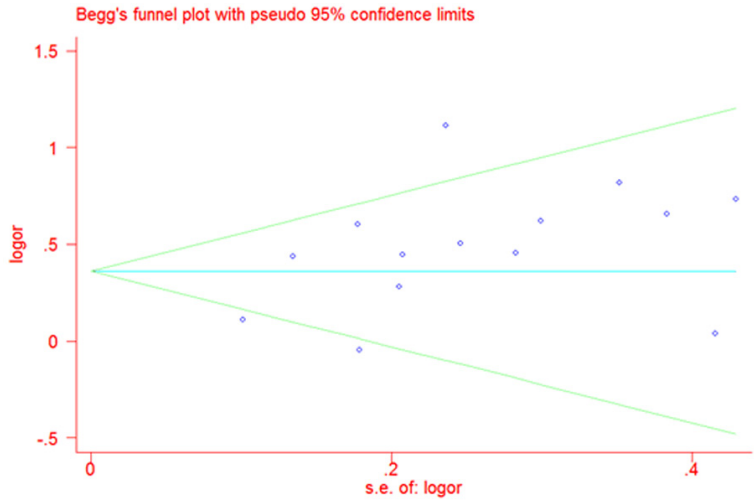


**Figure 4.** Begg's funnel plot for GG vs. GT+TT of the association between rs2279744 and HCC susceptibility to detect publication bias.

## Discussion

rs2279744, in the intronic promoter of *MDM2*, was associated with a significantly increased susceptibility of HCC in some populations. However, the results were inconsistent, for example, Leu and Yang et al. suggested that rs2279744 was not associated with HCC risk in several East Asian population [19, 22]. In the present study, after summarizing the relevant studies, we found *MDM2* rs2279744 showed significantly increased risk of hepatitis as well as HCC in the overall populations, and different ethnic subgroups, especially in the recessive model.

As a tumor suppressor, TP53 could bring about cell growth arrest and/or apoptosis in response to DNA damage and other stress responses [27]. It has been shown that attenuated p53 pathway resulting from genetic polymorphisms is associated with increased risk of carcinogenesis, such as *MDM2* rs2279744 [28, 29]. Bond et al. found *MDM2* rs2279744, with base change from T to G, could greatly enhance its binding affinity of the transcription factor Sp1, resulting in higher levels of *MDM2* RNA and protein [30]. The high

expression of *MDM2* protein results in the direct attenuation of p53 transcriptional activity, enabling damaged cell to escape the cell-cycle checkpoint and leading to tumorigenesis. This conclusion was in accordance with our present analysis result that *MDM2* rs2279744 was associated with increased risk of HCC.

Bond et al. suggested the presence rs2279744 GG associated with high expression of the *MDM2* transcript when compared with the levels seen in cells wild-type for rs2279744 TT. Besides, *MDM2* protein levels were also found to be significantly higher in cell lines for rs2279744 GG in their study [30]. And Hong and colleagues found that rs2279744 GG with significantly higher expression of *MDM2* mRNA in esophageal tissue than TT [31]. In the present study, we demonstrated that *MDM2* rs2279744 GG was significantly correlated with increased risk of HCC when compared with wild-type TT or under the recessive model of "GT+TT". Thus, the molecular biological findings of our analysis were in line with previous functional studies of *MDM2* rs2279744, which demonstrating the polymorphism could involve in the tumorigenesis of HCC.

We also showed a significant trend for the association between *MDM2* rs2279744 and hepatitis-related HCC susceptibility in all the comparison models. Shiratori et al. found the replication and proliferation of HCV was significantly enhanced when p53 expression is suppressed in vitro [32]. So, high expression of *MDM2* mRNA and protein levels result from *MDM2* polymorphism could lead to the direct suppression of p53 activity, which results in an unrestricted replication and proliferation of the virus inside hepatic cells and making them more vulnerable to HCC.

Several limitations in our present meta-analysis should be pointed out. First, the number of included studies were small, especially available studies about non-Asian. The limited sample size may influence the results of the present study and undermine the reliability of the statistical power. Thus, more studies are needed to confirm our data in future. Second, controls in some included studies were not healthy individuals, such as with chronic hepatitis, whom might have potential risks of developing HCC and bring about confounding effects on our present results.

Despite these limitations, results of this meta-analysis suggested that *MDM2* rs2279744 might influence HCC susceptibility. rs2279744 GG was significantly associated with higher occurrence of HCC as well as hepatitis-related HCC, especially in the recessive model, and could potentially be used to predict the development of HCC.

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## Disclosure of conflict of interest

None.

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