Association between MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270 polymorphisms and retinoblastoma susceptibility

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Abstract

Retinoblastoma (Rb) is the most common intra-ocular malignancy in children. The association of rs2279744, and rs937283 in MDM2 gene, and p21 rs1801270 polymorphism and RB development have been demonstrated. To provide a comprehensive assessment of and to clarify associations between the 3 SNPs (MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270) and the risk of RB, we performed a meta-analysis of all the eligible case-control studies. We searched English databases include PubMed, Embase, Google Scholar, and Cochrane Library, using an upper date limit of January 1, 2018. The association between MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270 polymorphisms and the risk of RB were estimated by calculating a pooled OR and 95% CI under a homozygote comparison, heterozygote comparison, dominant model, and recessive model. The statistical power analysis was performed using G*Power. Our meta-analysis showed a significant association between RB susceptibility and MDM2 rs2279744 recessive model (OR = 1.427, 95%CI: 1.107-1.840, P = .006, I^2 = 0%). Moreover, a significant link was observed between RB risk and MDM2 rs937283 homozygote comparison (OR = 0.471, 95%CI: 0.259-0.858, P = .014, I^2 = 0%) and recessive model (OR = 0.587, 95%CI: 0.410-0.840, P = .004, I^2 = 0%). However, no significant relationship between the p21 rs1801270 polymorphism and RB susceptibility was detected in any of the 4 models (P > .05). In conclusion, we found that significant association between the MDM2 rs2279744 polymorphism and increased RB risk, while MDM2 rs937283 polymorphism was associated with significantly decreased RB risk. However, as to the P21 rs1801270 polymorphism, a statistically significant association was not identified for RB.

Abbreviations: CI = confidence interval, MDM2 = mouse double minute 2 homolog, OR = odds ratios, p21 = cyclin-dependent kinase inhibitor 1, p53 = tumor protein p53, Rb = Retinoblastoma.

Keywords: meta-analysis, retinoblastoma, rs1801270, rs2279744, rs937283

1. Introduction

Retinoblastoma (Rb) is the most common intra-ocular malignancy in children and its incidence is approximately 1 case for every 15,000 to 28,000 live births.[1,2] Normally, RB presents at a young age, with about two - thirds of all patients diagnosed before 2 years of age.[3] Clinical presentations of RB include strabismus, leukocoria, red eye, nystagmus, and loss of binocularity depending on the tumor location.[4] The primarily treatment for RB are surgery and chemotherapy. Even if the curative effect and survival rate of children have been raised obviously, RB is still a serious threat to the health of children all over the world.[5] RB may develop rapidly during early childhood, thus it is vital to finding tumors early and preserving vision.[6]

Recently, researchers mainly focused on the identification of RB genetic biomarkers such as gene polymorphisms, microRNA, and lnRNA. Interestingly, some studies have shown that a series of other genes, such as cyclin-dependent kinase inhibitor 1 (p21), tumor protein p53 (p53), mouse double minute 2 homolog (MDM2), and MDM4, may influence the development of RB. p21 rs1801270 polymorphism can produce a C to A transversion and cause a substitution from serine to arginine, affecting the DNA binding zinc finger domain of the protein.[7] Moreover, p21 is the primary protein that is upregulated by activated p53 in response to DNA damage.[8] MDM2 gene is an important negative regulator of the p53 suppressor gene, promoting the degradation of p53 through its E3 ubiquitin ligase activity.[9] The association of 2 single nucleotide polymorphisms (SNPs) (rs2279744 and rs937283) in MDM2 gene and RB development have been demonstrated.[10]

To provide a comprehensive assessment and to clarify associations between the 3 SNPs (MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270) and the risk of RB, we performed a meta-analysis of all the eligible case-control studies.

2. Materials and methods

This systematic review and meta-analysis were conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[11] The secondary research

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The authors declare no conflicts of interest.

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was conducted in our meta-analysis by reviewing previous publications without linking to any human subjects, thus, ethical approval is not required.

2.1. Literature search strategy and selection criteria

To conduct a literature search, we searched English databases include PubMed, Embase, Google Scholar, and Cochrane Library, using an upper date limit of January 1, 2018 with the following strategy: (Retinoblastoma OR Retinal Neuroblastoma OR Retinal Glioma OR Sporadic Retinoblastoma) AND (rs1801270 OR p21 Ser31Arg) OR (rs2279744 OR MDM2 SNP T309G) OR (rs937283 OR MDM2 SNP G2164A). All the included studies must meet the following criteria: studies involving the association between MDM2 rs2279744, MDM2 rs937283 and p21 rs1801270 polymorphisms and risk of RB; case-control studies based on human; studies published in English; studies with usable and sufficient original data for estimating odds ratios (OR) and their 95% confidence interval (CI). The main exclusion criteria were: duplicate articles; reviews and meta-analysis; not case-control studies; animal studies; not relevant to specific polymorphisms or RB; no sufficient and eligible raw data even after contacting the authors.

2.2. Literature data extraction

The following data were extracted from each included studies independently by 2 investigators: the first author's name, year of publication, country of origin, ethnicity of study population, source of control, patient number of cases and controls, and the association between the 3 SNPs (MDM2 rs2279744, MDM2 rs937283 and p21 rs1801270) and the risk of RB. The extracted data were compared, and discrepancies were solved by consensus.

2.3. Statistical analysis

The association between MDM2 rs2279744 polymorphism and the risk of RB was estimated by calculating a pooled OR and 95% CI under a homozygote comparison (TT vs GG), heterozygote comparison (TG vs GG), dominant model (TT+TG vs GG) and recessive model (TT vs TG+GG). To determine the link between MDM2 rs937283 polymorphism and the RB risk, homozygote comparison (AA vs GG), heterozygote comparison (AG vs GG), dominant model (AA+AG vs GG) and recessive model (AA vs AG+GG) were also operated. Similarly, homozygote comparison (CC vs AA), heterozygote comparison (CA vs AA), dominant model (CC+CA vs AA) and recessive model (CC vs CA+AA) were also conducted to explore the relationship between P21 rs1801270 polymorphism and the susceptibility to RB. The fixed-effects model or random-effects model was selected depending on whether or not heterogeneity existed among studies. The Cochrane Q test (ie, the chi-squared test) was applied to estimate heterogeneity among the included relevant studies. If $I^2 < 50\%$, the fixed effects model was applied. Otherwise, the random-effects model was chosen.[12] Furthermore, a prediction interval was calculated under the random-effects model, because it can provide a predicted range for the true effect size.[13–15] However, studies less than 3 were not calculated prediction interval. It is worth mentioning that publication bias was only effective when there are at least 10 relevant studies exist. Otherwise, publication bias was underpowered and would have led to unreliable results.[16] We therefore decided to quit

publication bias in this meta-analysis due to the limited included studies (only 5 trials). All meta-analyses were conducted on STATA12.0 (Stata Corporation, College Station, TX, USA). In addition, statistical power analysis was performed using G*Power 3.1.9.2 with an α level of 5%.[17]

3. Results

3.1. Included studies and the characteristics

Figure 1 showed the process of acquiring eligible studies. 2587 records were identified from PubMed, Embase, Google Scholar, and Cochrane Library. After title and abstract evaluation, 2311 duplicates were removed and 210 were excluded for not reporting the 3 SNPs (MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270) and the risk of RB. Thus, 66 unique studies left for more detailed evaluation. We found that 37 studies were not original research and 20 studies did not involve humans by reading the full text. We therefore have 9 potential studies for further analyses, however, 4 trials were removed for no usable data. Finally, 5 articles with 1526 patients were included in this meta-analysis.

According to the polymorphisms investigated, the characteristics of the included studies were summarized in Table 1. Four studies involved the MDM2 rs2279744,[10,18–20] 2 studies [18,19] showed a lower risk in RB and the rest of studies [10,20] showed no significant association between MDM2 rs2279744 polymorphisms and RB risk. Two studies estimated MDM2 rs937283 [10,19] with 1 trial [10] indicated a higher risk of RB and another trial [19] showed MDM2 rs937283 not link with RB risk. Meanwhile, 2 studies investigated p21 rs1801270 polymorphisms [20,21] susceptibility to RB, 1 study [21] observed higher RB susceptibility and the remaining trial [20] showed no significant association between RB susceptibility and p21 rs1801270 polymorphisms. Among the included studies, 2 from China,[10,20] 2 from Brazil,[19,21] and 1 from Italy.[18] Two studies investigated Han Chinese[10,20] and 1 trial involved Caucasian, Mullato or Black,[19] while the ethnicity of 2 studies was not available.[18,21] The included trials were all case-control studies, the case group all consist of RB patients, and the control group included unrelated individuals,[18] unrelated healthy adults,[19,21] healthy adults [20] and normal control.[10] All included studies obtained blood sample from each recruited individual for genomic DNA extraction, and were all assessed by polymerase chain reaction (PCR).

3.2. MDM2 rs2279744, MDM2 rs937283 and p21 rs1801270 polymorphisms and susceptibility to RB

We pooled 4 studies [10,18–20] involving MDM2 rs2279744 to evaluate the RB risk associated with MDM2 rs2279744 polymorphisms. The meta-analysis showed a significant statistical association between RB susceptibility and MDM2 rs2279744 recessive model (TT vs TG+GG) (OR (95%CI) = 1.427 (1.107–1.840), P = .006, Figure 2D, 95% prediction interval: 0.82–2.50) with the fixed-effects model (P = 0.409, $I^2 = 0\%$), while no statistical significance was detected in the 3 genotypes of homozygote comparison (TT vs GG) (OR (95%CI) = 1.307 (0.929–1.841), P = .125, Figure 2A, 95% prediction interval: 0.40–4.45) with the fixed-effects model (P = .276, $I^2 = 22.5\%$), heterozygote comparison (TG vs GG) (OR (95%CI) = 0.935 (0.691–1.265), P = .664, Figure 2B, 95% prediction interval: 0.48–1.82) with the fixed-effects model (P = .679, $I^2 = 0\%$), and
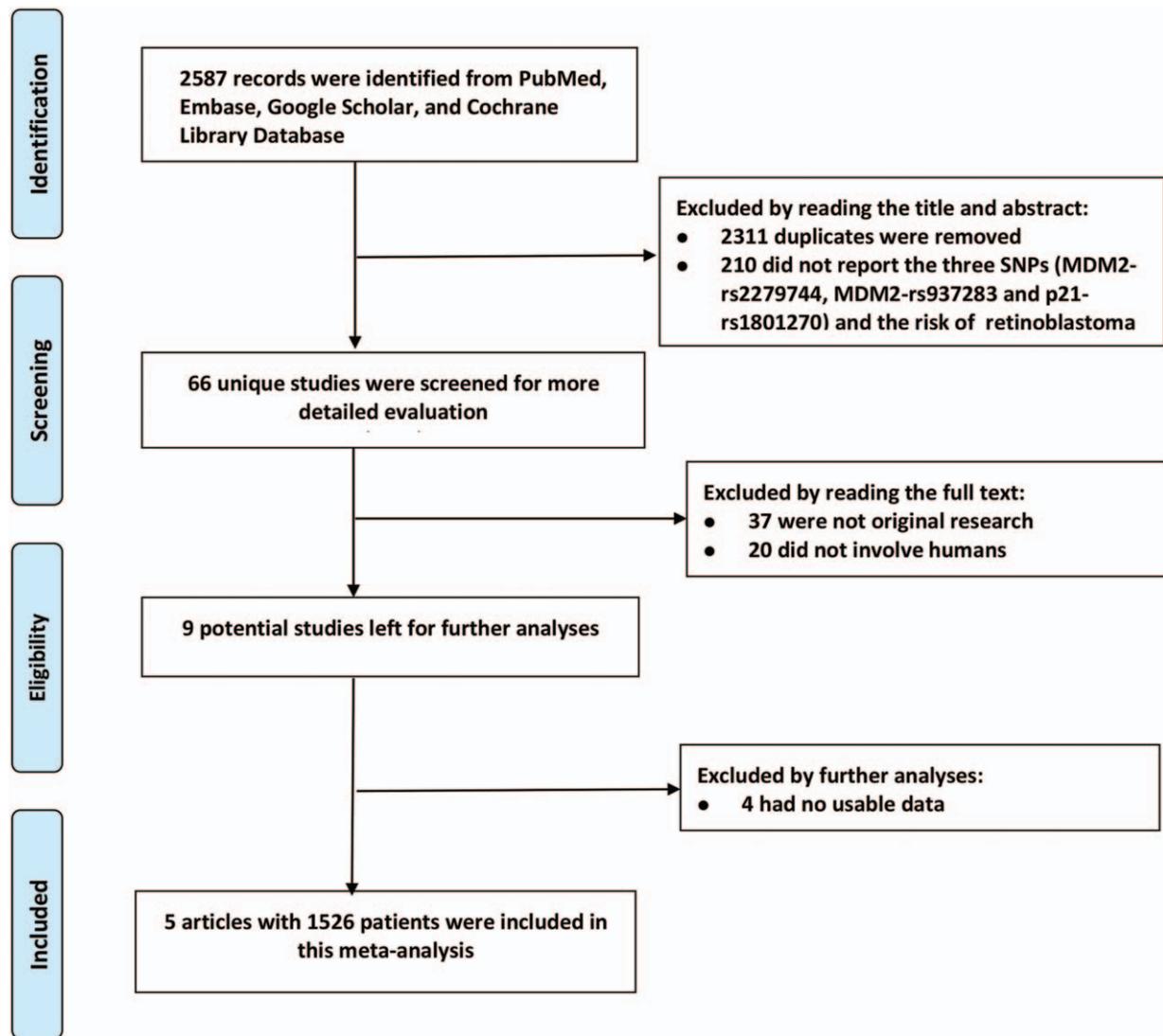
Figure 1. The process of identifying included studies.

dominant model (TT+TG vs GG) (OR $(95\%\,CI)$ = 1.042 (0.786–1.382), P=.774, Figure 2C, 95% prediction interval: 0.55–1.96) with the fixed-effects model (P=.388, I^2=0.7%). The results indicated that the MDM2 rs2279744 polymorphisms were significantly associated with susceptibility to RB.

Two trials [10,19] were pooled to estimate the association between RB risk and MDM2 rs937283 polymorphisms, a significant statistical association was observed between lower RB risk and MDM2 rs937283 homozygote comparison (AA vs GG) (OR $(95\%\,CI)$ = 0.471 (0.259–0.858), P=.014, Fig. 3A) with the fixed-effects model (P=.581, I^2=0%) and recessive model (AA vs AG+GG) (OR $(95\%\,CI)$ = 0.587 (0.410–0.840), P=.004, Fig. 2D) with the fixed-effects model (P=.334, I^2=0%). However, no significant statistical link was found in the 2 genotypes of heterozygote comparison (AG vs GG) (OR $(95\%\,CI)$ = 0.741 (0.406–1.354), p=0.330, Fig. 3B) with the fixed-effects model (P=.964, I^2=0%) and dominant model (AA+AG vs GG) (OR $(95\%\,CI)$ = 0.581 (0.329–1.025), P=.061, Fig. 3C) with the fixed-effects model (P=.708, I^2=0%). The meta-analysis showed a statistical significance between lower RB risk and MDM2 rs937283 polymorphisms.

To investigate the relationship between p21 rs1801270 polymorphisms and susceptibility to RB, we combined 2 trials [20,21] based on homozygote comparison (CC vs AA), heterozygote comparison (CA vs AA), dominant model (CC+CA vs AA) and recessive model (CC vs CA+AA), the pooled ORs $(95\%\,CIs)$ were (1.242 (0.716-2.156), P=.441, Fig. 4A) with the fixed-effects model (P=.437, I^2=0%), (1.077 (0.651–1.781), P=.774, Fig. 4B) with the fixed-effects model (P=.699, I2=0%), (1.115 (0.694–1.792), P=.654, Fig. 4C) with the fixed-effects model (P=.745, I^2=0%) and (0.824 (0.323–2.103), P=.685, Fig. 4D) with the random-effects model (P=.008, I^2=85.7%), respectively. No significant statistical relationship between the p21 rs1801270 polymorphism in RB susceptibility was detected in any of the 4 models, which indicated that p21 rs1801270 polymorphism was not link with the risk of RB. All results of the analysis were shown in Table 2.

3.3. Power analysis

We calculated the statistical power analysis to reassess the available data when an alpha of 0.05 was assigned. As shown in

Table 1

Characteristic of Included Studies.

					MDM2 rs2279744						
					Case			Control			
First Author	Year	Country	Ethnicity	Source of Control	TT	TG	GG	TT	TG	GG	Association*
Epistolato MC	2011	Italy	Not available	Unrelated individuals	49	49	13	100	165	42	Lower Risk
de Oliveira Reis AH	2012	Brazil	Caucasian, Mullato or Black	Unrelated, healthy adults	53	44	7	37	53	14	Lower Risk
Chen R	2015	China	Han Chinese	Healthy adults	34	75	59	36	88	60	Not significant
Jiao Y	2016	China	Han Chinese	Normal control	37	59	41	34	73	43	Not significant

					MDM2 rs937283						
					Case			Control			
First Author	Year	Country	Ethnicity	Source of Control	AA	AG	GG	AA	AG	GG	Association*
de Oliveira Reis AH	2012	Brazil	Caucasian, Mullato or Black	Unrelated, healthy adults	37	51	16	45	48	11	Not significant
Jiao Y	2016	China	Han Chinese	Normal control	60	59	18	91	48	11	Higher Risk

					p21 rs1801270						
					Case			Control			
First Author	Year	Country	Ethnicity	Source of Control	CC	CA	AA	CC	CA	AA	Association*
Carvalho IN	2013	Brazil	Not available	Unrelated, healthy adults	85	52	4	90	27	3	Higher Risk
Chen R	2015	China	Han Chinese	Healthy adults	51	81	36	46	95	44	Not significant

* The association between the 3 SNPs (MDM2 rs2279744, MDM2 rs937283 and p21 rs1801270) and the risk of RB.

Table 2, the statistical power ranged from 9.3% to 54.0% for MDM2 rs2279744 analysis. For MDM2 rs937283 analysis, the statistical power ranged from 14.4% to 78.2%. The power of P21 rs1801270 analysis ranged from 4.5% to 15.5%.

4. Discussion

Early in 1809, RB was first described by the Scottish surgeon James Wardrop, as white brain-like intraocular tumors of retinal origin.[22] With social and economic development, the under-
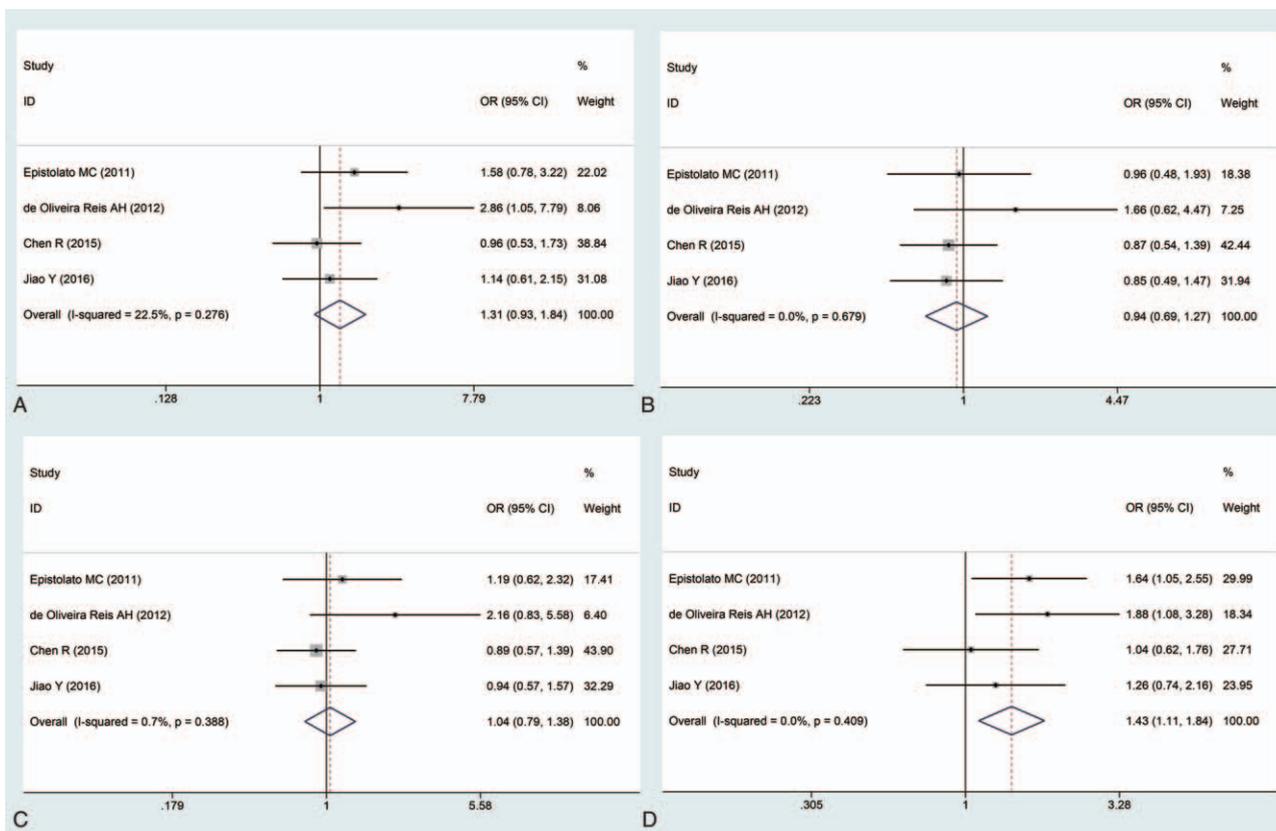
Figure 2. (A) The forest plot of MDM2 rs2279744 homozygote comparison (TT vs GG) and RB risk; (B) The forest plot of MDM2 rs2279744 heterozygote comparison (TG vs GG) and RB risk; (C) The forest plot of MDM2 rs2279744dominant model (TT+TG vs GG) and RB risk; (D) The forest plot of MDM2 rs2279744recessive model (TT vs TG+GG) and RB risk. Rb = Retinoblastoma.
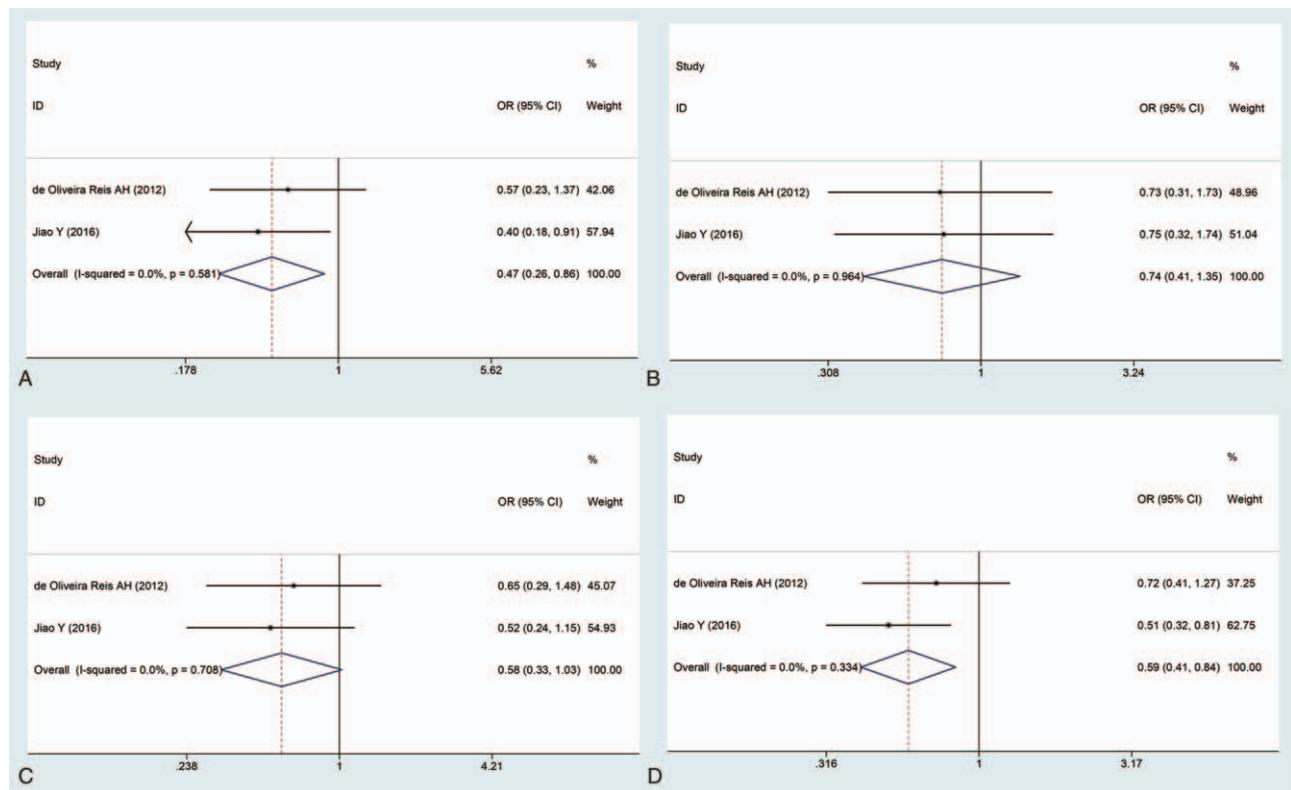
Figure 3. (A) The forest plot of MDM2 rs937283 homozygote comparison (AA vs GG) and RB risk; (B) The forest plot of MDM2 rs937283 heterozygote comparison (AG vs GG) and RB risk; (C) The forest plot of MDM2 rs937283 dominant model (AA+AG vs GG) and RB risk; (D) The forest plot of MDM2 rs937283 recessive model (AA vs AG+GG) and RB risk. Rb = Retinoblastoma.

standing of the mechanism of RB is deeper day by day. Importantly, the gene plays an important role in the development of RB. Almost half of the children with RB have a hereditary genetic defect associated with RB.[23] Although several genetic studies have reported the correlation between MDM2 rs2279744 polymorphism, MDM2 rs937283 polymorphism, or p21 rs1801270 variant and the risk of RB, these results were inconclusive since they are performed in an individual medical center with small sample size and in different ethnicities. Therefore, it is important to perform a meta-analysis of all eligible studies to clarify the effects of MDM2 rs2279744 polymorphism, MDM2 rs937283 polymorphism, or P21 rs1801270 variant on risk of RB.

To the best of our knowledge, the meta-analysis in this study is the largest to study the associations between MDM2 rs2279744, MDM2 rs937283, or P21 rs1801270 polymorphisms and RB risk. In our meta-analysis, based on the database of publications in respect of the MDM2 rs2279744 polymorphism, MDM2 rs937283 polymorphism, and the P21 rs1801270 polymorphism, among which there are 4 studies including 520 cases and 745 controls for MDM2 rs2279744 polymorphism, 2 studies including 241 cases and 254 controls for MDM2 rs937283 polymorphism, and 2 studies including 309 cases and 305 controls for P21 rs1801270 polymorphism respectively. An increased risk of RB was found for the MDM2 rs2279744 polymorphism. Likewise, we observed MDM2 rs937283 polymorphism was significantly associated with a decreased RB risk. Interestingly, as to the P21 rs1801270 polymorphism, a statistically significant association was not identified for RB.

MDM2 rs2279744 (also known as MDM2 SNP T309G) is a G/T single-nucleotide variation on human chromosome 12. It can influence the binding of the transcription factor, Sp1. Sp1 binds with higher affinity to the G allele than to the T allele, which accounts for increased transcription of the MDM2 gene and higher expression levels of MDM2 protein, and thereby inhibits the function of p53 pathway in the prevention of tumor formation.[24] Our results evaluated MDM2 rs2279744 polymorphism may be a risk factor for the development of RB. Prediction intervals were calculated for MDM2 rs2279744. The results of prediction intervals are wide, suggesting that future research may demonstrate benefit, disadvantage, or not demonstrate any statistically significant difference.[25] Similar to our analysis, some meta-analysis demonstrated that MDM2 rs2279744 is associated with squamous cell carcinoma,[26] colorectal cancer,[27] endometrial cancer,[28] and hepatocellular carcinoma.[29] But 2 meta-analyses indicated that MDM2 rs2279744 polymorphism cannot be considered as genetic risk factors for osteosarcoma,[30] and prostate cancer.[27] More interestingly, Xie et al[31] found MDM2 rs2279744 polymorphism has no influence on bladder cancer risk in Asians, but this single nucleotide polymorphism may be associated with genetic susceptibility of bladder cancer among Caucasians. Considering the above results, we think that MDM2 rs2279744 polymorphism may have tumor suppressor functions under certain conditions. Thus, gene-environment and gene-gene interactions regulate carcinogenesis, and the presence of some other causal factors until now unrealized evaluate an association between MDM2 rs2279744 polymorphism and RB development.
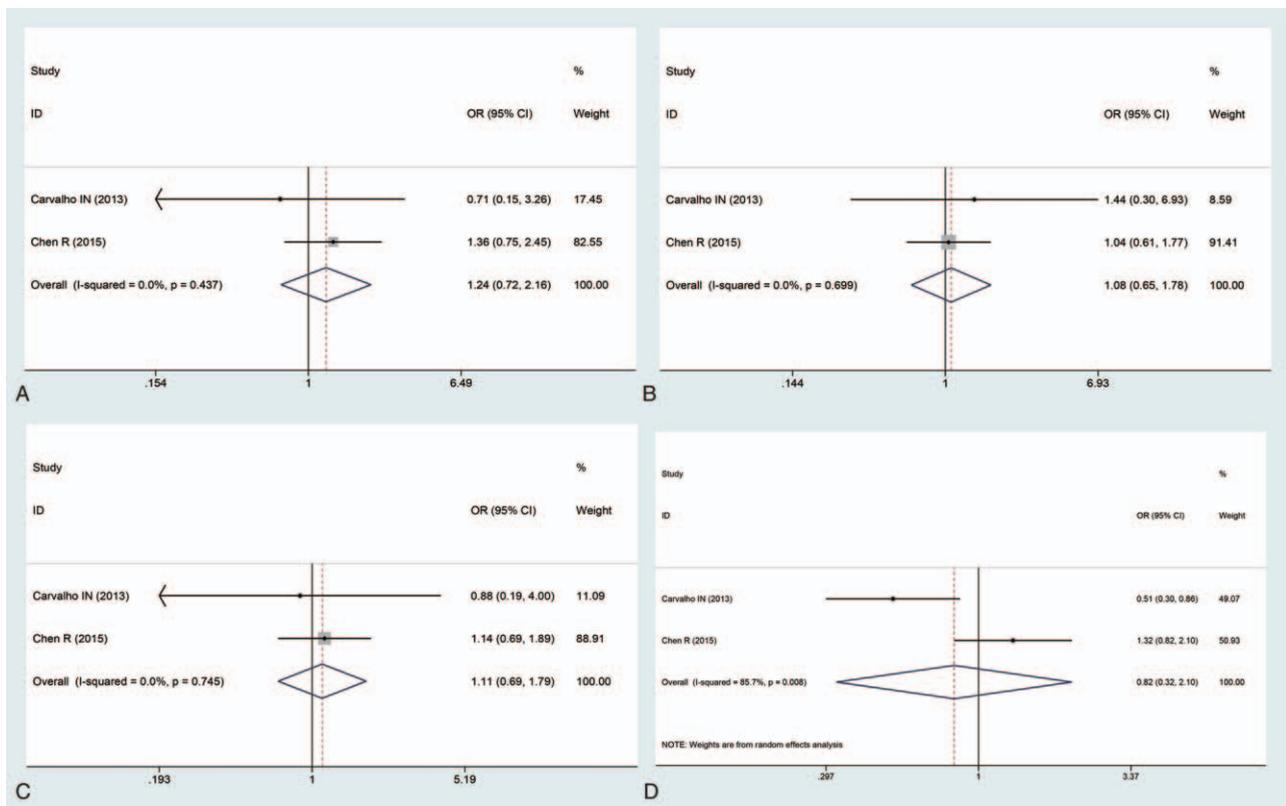
Figure 4. (A) The forest plot of p21 rs1801270 homozygote comparison (CC vs AA) and RB risk; (B) The forest plot of p21 rs1801270 heterozygote comparison (CA vs AA) and RB risk; (C) The forest plot of p21 rs1801270 dominant model (CC+CA vs AA) and RB risk; (D) The forest plot of p21 rs1801270 recessive model (CC vs CA+AA) and RB risk. Rb = Retinoblastoma.

Table 2
Results of Analysis.

MDM2-rs2279744		Homozygote Comparison TT vs GG	Heterozygote Comparison TG vs GG	Dominant Model (TT+TG) vs GG	Recessive Model TT vs (TG+GG)	Association*
Heterogeneity	I^2 (%)	22.5	0	0.7	0	Higher Risk
	P	.276	.679	.388	.409	
Meta-Analysis	OR (95%CI)	1.307 (0.929–1.841)	0.935 (0.691-1.265)	1.042 (0.786–1.382)	1.427 (1.107–1.840)	
	P	0.125	0.664	0.774	0.006	
	prediction interval	0.40–4.45	0.48-1.82	0.55–1.96	0.82–2.50	
Power		9.3%	33.6%	10.8%	54.0%	

MDM2-rs937283		Homozygote Comparison AA vs GG	Heterozygote Comparison AG vs GG	Dominant Model (AA+AG) vs GG	Recessive Model AA vs(AG+GG)	Association*
Heterogeneity	I^2 (%)	0	0	0	0	Lower Risk
	P	.581	.964	.708	.334	
Meta-Analysis	OR (95%CI)	0.471 (0.259–0.858)	0.741 (0.406–1.354)	0.581 (0.329–1.025)	0.587 (0.410–0.840)	
	P	0.014	0.33	0.061	0.004	
Power		70.3%	14.4%	41.2%	78.2%	

P21-rs1801270		Homozygote Comparison CC vs AA	Heterozygote Comparison CA vs AA	Dominant Model (CC+CA) vs AA	Recessive Model CC vs (CA+AA)	Association*
Heterogeneity	I^2 (%)	0	0	0	85.7	Not Significant
	P	.437	.699	.745	.008	
Meta-Analysis	OR (95%CI)	1.242 (0.716–2.156)	1.077 (0.651–1.781)	1.115 (0.694–1.792)	0.824 (0.323–2.103)	
	P	0.441	0.774	0.654	0.685	
Power		9.1%	15.5%	12.8%	4.5%	

CI=confidence interval, OR=odds ratio; a, the association between the 3 SNPs (MDM2-rs2279744, MDM2-rs937283 and p21-rs1801270) and the risk of RB.

MDM2 rs937283 (also known as SNP G2164A) polymorphism could lead to an A to G base change at the 2164 nucleotide in the promoter region of MDM2 gene. Jiao et al[10] suggested that the MDM2 rs937283 polymorphism is a novel functional SNP both in vitro and in vivo as well as a biomarker for poor prognosis in RB. However, our meta-analysis proved that MDM2 rs937283 polymorphism was significantly associated with a decreased RB risk. A possible explanation is that our meta-analysis included more studies that have more patients.

The p21 rs1801270 (also named p21 Ser31Arg), which occurs in codon 31, results in an amino acid substitution of arginine for serine. This polymorphism is located in a highly conserved region of p21 and is expected to affect its molecular function.[32] Prior study has shown an association between the p21 rs1801270A allele and a decreased risk for cervical cancer in a population of Chinese women.[33] However, Taghavi et al[34] suggest that p21 rs1801270 is not genetic susceptibility biomarker for esophageal squamous cell carcinoma. Similarly, our analysis indicated that p21 rs1801270 is not the risk of RB development. A possible reason for this may be that the mechanism of carcinogenesis may differ between different cancer sites and the p21 rs1801270 genetic variants may exert multiple effects in different cancers.[35]

Notably, our analysis is not without limitations. First, only 5 studies were included for the meta-analysis, the case number included in our analysis is relatively small. Moreover, the statistical power for each analysis is not high. Second, gene-gene, gene-environment (including age, environmental factors, lifestyle, and some other factors) and within-gene interactions may modulate RB risk, and therefore should be identified in the future study. Finally, since the included studies were only written in English, the language bias is inevitable.

In conclusion, our meta-analysis found that significant association between the MDM2 rs2279744 polymorphism and increased RB risk. Moreover, MDM2 rs937283 polymorphism was associated with significantly decreased RB risk. Interestingly, as to the P21 rs1801270 polymorphism, a statistically significant association was not identified for RB. Considering the above-mentioned limitations, more adequately powered and well-designed studies are required to verify this conclusion.

Author contributions

Conceptualization: Weihua Yang.
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Formal analysis: Yun Wang.
Methodology: Qixin Cao and Xiaohui Song.
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Writing – original draft: Qixin Cao, Yun Wang, and Weihua Yang.
Writing – review and editing: Weihua Yang.

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