

The mouse double minute 2 309T>G polymorphism and retinoblastoma risk: A meta-analysis

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Abstract:

PURPOSE: Mouse double minute 2 (MDM2) homolog is a protein that in humans is encoded by the MDM2 gene. It is expressed in retinoblastoma (Rb) cells and acts as a key negative regulator of the p53 tumor suppressor gene. Several studies have investigated the association of Rb with MDM2 309T>G polymorphism, but the results were conflicting. To derive a more precise estimation of the association, we performed a meta-analysis of the relationship between MDM2 309T>G polymorphism with Rb in all published studies.

METHODS: Published literature from PubMed and other databases were retrieved. All the reported studies evaluating the association between MDM2 309T>G polymorphism and Rb risk were included. The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using the fixed-effect model. A total of four case-control studies, including 520 cases and 745 controls were included.

RESULTS: This meta-analysis found that MDM2 309T>G polymorphism was significantly associated with Rb risk in the dominant model, TG+GG versus TT (OR = 1.43, 95% CI = 1.11–1.84, $P = 0.006$).

CONCLUSION: The present meta-analysis suggested that MDM2 309T>G polymorphism has a significant association with increased Rb risk.

Keywords:

Meta-analysis, mouse double minute 2, polymorphism, retinoblastoma

INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular malignancy of childhood. The incidence has been reported in approximately 1 in 18,000 live births worldwide.^[1,2] Leukocoria (most frequent), poor vision, redness, squint, or proptosis are the symptoms of Rb.^[2] The majority of children have been diagnosed before 5 years of age. The disease may be unilateral (only one eye affected) or bilateral (tumor development in both eyes); bilateral involvement has been seen in one-third of cases. The gene in the chromosome region 13q14 has been identified as the human Rb susceptibility (RB1) gene.^[3] The complete loss of RB1 activates p53-mediated apoptosis and does not confer a growth advantage.^[4] Murine double minute family proteins such as mouse

double minute 2 (MDM2) and MDM4, which are both expressed in Rb cells,^[5] are key negative regulators of the p53 pathway. The amplification of these proteins inhibits p53-mediated transactivation activity by targeting p53 for proteasomal degradation. Thereby, bypassing p53-mediated apoptosis and conferring a cell growth advantage when RB1 expression is lost. It also promotes the degradation of Rb protein by ubiquitin-dependent or -independent mechanisms.^[6-8] Therefore, the changes in the expression levels of MDM2 may be associated with the variable phenotypic expression of Rb.

MDM2 gene is highly polymorphic, and many single nucleotide polymorphisms (SNPs) have been observed. An SNP located at nucleotide 309 in the promoter region of MDM2, i.e., 309T>G (rs2279744), enhances the transcription and accumulation of MDM2 protein resulting in the attenuation of the p53 pathway. It has been reported that the

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MDM2 SNP309 G allele is associated with many other cancers, including Li-Fraumeni,^[9] colorectal cancer,^[10] lung cancer.^[11] etc. Moreover, a significant association between MDM2 309T>G polymorphism and Rb development has been found in predisposed patients with RB1 mutations.^[12,13] However, some other studies show no association between MDM2 309T>G polymorphism and Rb.^[14-16] These studies revealed a conflicting conclusion, probably due to the relatively small size of subjects, since individual studies are usually underpowered in detecting the effect of low penetrance genes. Therefore, in this study, we conducted a meta-analysis to investigate the association between MDM2 309T>G polymorphism and the risk for Rb.

METHODS

Identification and eligibility of relevant studies

We have conducted a literature survey in the PubMed, EMBASE, Cochrane Library, Google, Dogpile, and CBM database using the following terms and keywords: “MDM2,” “Mouse double minute 2 homolog,” “MDM2 SNP309,” “MDM2 309T>G,” “rs2279744 polymorphism,” and “human retinoblastoma.” The literature survey helped us to find the studies that examined the association of MDM2 309T>G polymorphism with human Rb. A manual search from other sources has identified additional studies (e.g., Web of Knowledge), references of original studies, or review articles on this topic.

Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: (1) association shown between MDM2 309T>G and Rb risk; (2) case-control design; (3) available phenotype or allele frequencies of MDM2 309T>G in cases and controls; (4) the literature having a comprehensive statistical index, sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (5) papers published in English; and (6) all the studies included were according to tenets of the Declaration of Helsinki.

The primary reasons for exclusion of studies were as follows: (1) studies which were not possible to extract data from the published results; (2) studies that did not report appropriate outcomes; (3) case-only studies; (4) all three genotype frequency missing; and (5) family-based studies.

Data extraction

The authors independently reviewed all the potentially relevant papers by assessing the eligibility of each article and abstracting data with standardized data-abstraction forms. For each study, the following information was extracted: name of the first author; publication year; country; ethnicity; genotyping methods; source of samples; sample size (numbers of cases and controls); and the minor allele frequency in the controls. The studies included in this meta-analysis on the association of Rb with MDM2 309T>G polymorphism are shown in Table 1. The MDM2 309T>G

polymorphism genotype distributions from each study are presented in Table 2.

Statistical analysis

Data were analyzed by STATA software, version 13.0 (STATA Corp., College Station, TX, USA). The association between MDM2 309T>G polymorphism and Rb risk was estimated by calculating pooled ORs and 95% CIs. The pooled OR and 95% CI were calculated using a random-effects model if the case of heterogeneity more than 50%, on the other hand, a fixed-effect model was applied if heterogeneity was <50% measured by the I^2 method. The genetic models, including the allelic (T vs. G), dominant (TG + GG vs. TT), recessive (TT + TG vs. GG), were used to analyze the association.

RESULTS

Association of mouse double minute 2 309T>G polymorphism with retinoblastoma

This meta-analysis included four eligible studies on the association of the MDM2 309T>G polymorphism with Rb. The fixed-effect model was used in allele model, dominant model, and recessive model. A significant association was found between MDM2 309T>G polymorphism and Rb risk in dominant model, TG + GG versus TT (OR = 1.43, 95% CI = 1.11–1.84, $P = 0.006$) [Figure 1]. However, there was no significant association found in allelic, T versus G (OR = 0.85, 95% CI = 0.72–1.00, $P = 0.051$) [Figure 2] and recessive model, TT + TG versus GG (OR = 0.96, 95% CI = 0.72–1.27, $P = 0.774$) [Figure 3].

Sensitivity analysis and publication bias

Individual studies were consecutively excluded in the sensitivity analysis to investigate whether the obtained results were robust. The sensitivity analysis showed that the results obtained in the meta-analysis were statistically robust because the corresponding combined ORs in all of the separate subgroup analyses were relatively stable when deleting any individual study.

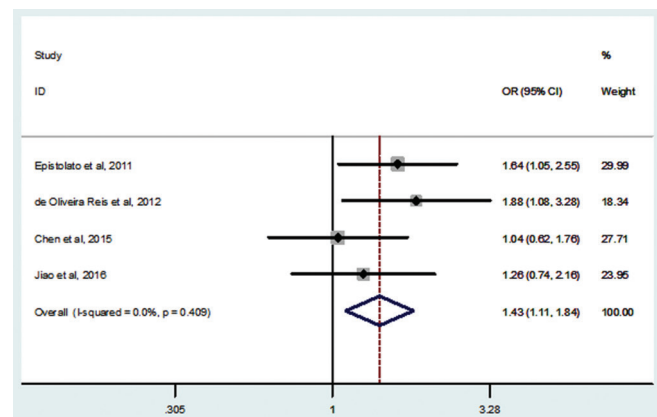


Figure 1: Meta-analysis under dominant model (TG + GG vs. TT) for the association between retinoblastoma risk and the mouse double minute 2 309T>G polymorphism

Table 1: Characteristics of studies included in the mouse double minute 2 homolog 309T >G meta-analysis

Study	Years	Country	Ethnicity	Genotyping method	Sample	Case	Control	References
Epistolato <i>et al.</i>	2011	Italy	Caucasian	PCR-sequencing	Blood	111	307	PMID: 21814224
de Oliveira Reis <i>et al.</i>	2012	Brazil	Brazilian	PCR-RFLP	Blood	104	104	PMID: 22180099
Chen <i>et al.</i>	2015	China	Asian	MALDI-TOF mass spectrometry	Blood	168	184	PMID: 26289323
Jiao <i>et al.</i>	2016	China	Asian	TaqMan® SNP genotyping assays	Blood	137	150	PMID: 27506496

PCR=Polymerase chain reaction; RFLP=Restriction fragment length polymorphism; MALDI=Matrix-assisted laser desorption/ionization; TOF=Time-of-flight; SNP=Single nucleotide polymorphisms

Table 2: Mouse double min 2 homolog 309T >G polymorphism genotype distribution of each study included in the meta-analysis

Author/year	Genotype frequency						Allele frequency				Dominant model				Recessive model			
	Cases			Controls			Cases		Controls		Cases		Controls		Cases		Controls	
	TT	TG	GG	TT	TG	GG	T	G	T	G	TT	TG+GG	TT	TG+GG	GG	TT+TG	GG	TT+TG
Epistolato <i>et al.</i> , (2011)	49	49	13	100	165	42	147	75	365	249	49	62	100	207	13	98	42	265
de Oliveira Reis <i>et al.</i> , (2012)	53	44	7	37	53	14	150	58	127	81	53	51	37	67	7	97	14	90
Chen <i>et al.</i> , (2015)	34	75	59	36	88	60	143	193	160	208	34	134	36	148	59	109	60	124
Jiao <i>et al.</i> , (2016)	37	59	41	34	73	43	133	141	141	159	37	100	34	116	41	96	43	107

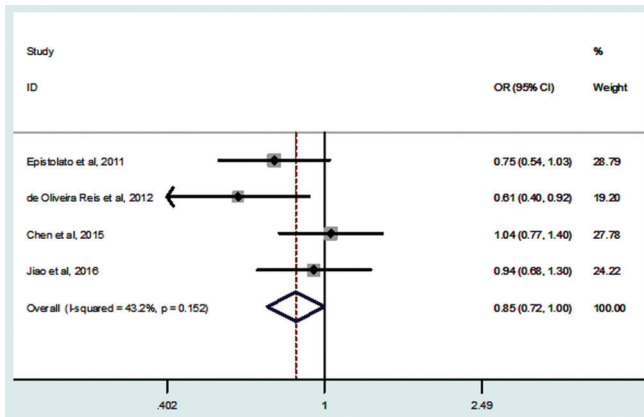


Figure 2: Meta-analysis under allelic model (T vs. G) for the association between retinoblastoma risk and the mouse double minute 2 309T>G polymorphism

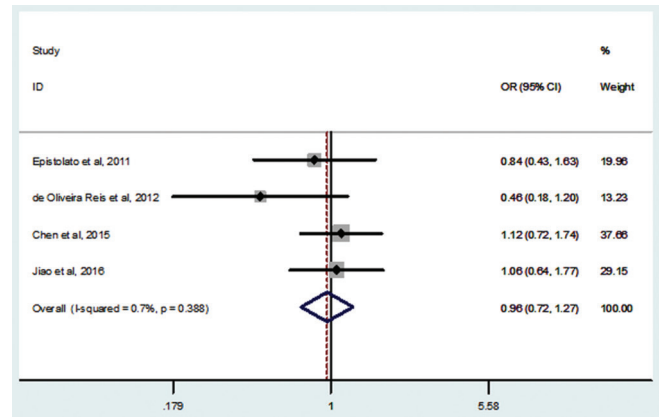


Figure 3: Meta-analysis under recessive model (TT + TG vs. GG) for the association between retinoblastoma risk and the mouse double minute 2 309T>G polymorphism

DISCUSSION

In the present study, we have reviewed all available published studies and performed a meta-analysis to examine the association between MDM2 309T>G polymorphism and susceptibility to Rb. It is the first study where we have examined all the possible models (dominant, recessive, and allelic levels) to validate our results. Our meta-analysis showed that there was a significant association between MDM2 309T>G and Rb risk in the dominant model. The previously reported studies in literature did not observe the statistical significance,^[14-16] however increasing the power using the meta-analysis approach observes the statistically significant association.

The deviation most likely indicates a genotyping assay problem with an erroneous gain/loss of homozygous genotypes. The commonly used polymerase chain reaction-restriction fragment length polymorphism analysis for genotyping is reported to have poor accuracy and reproducibility^[17] and may underlie this finding. Conversely, the effects of sample selection and differences in

biological and environmental complexity between samples could also hinder efforts to replicate association in most of the studies which are statistically underpowered. The meta-analysis helps researchers to deal with the diversity of the published data but, in general, cannot do justice to complex human diseases, which involve multiple genetic and environmental determinants.^[18] However, in the present study of total combined data, there is a significant association found in the dominant model with Rb risk. Therefore, the different results across studies may result from small sample size and/or genotyping technique rather than ethnic differences. Since the studies included were very limited, it is necessary to validate the association between MDM2 309T>G polymorphism and Rb risk in future studies. A well-designed meta-analysis can provide valuable information for researchers, policymakers, and clinicians.

CONCLUSION

We systematically reviewed the association of MDM2 309T>G polymorphism with the risk of Rb. Furthermore, the study has

been performed using all available data of a highly studied polymorphism (rs2279744) up to the best of our knowledge. The present meta-analysis suggested that MDM2 309T>G polymorphism has a significant association with increased Rb risk. More epidemiological studies are needed to validate this conclusion further.

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Conflicts of interest

There are no conflicts of interest.

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