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ORIGINAL INVESTIGATION

MDM2 gene polymorphisms and risk of classic Kaposi's sarcoma among Iranian patients

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Abstract A single-nucleotide polymorphism (SNP) in the promoter region of MDM2 (SNP309T>G, rs2279744) has been shown to increase the expression of the MDM2 protein in various cancer types. However, only one study has analyzed the role of the MDM2 polymorphism in the development of Kaposi's sarcoma (KS). The association of MDM2 SNP309 with classic KS risk was evaluated in 79 Iranian patients with classic KS and 123 healthy controls. The MDM2 SNP309 was genotyped using PCR and restriction fragment length polymorphism methods. No significant correlation was found between the SNP309 polymorphism in MDM2 promoter and classic KS risk. There was no significant correlation between gender and disease stage. However, a significant association was found between SNP309 GG genotype and younger age (≤50 years) (odds ratio 9.5, 95% confidence intervals 1.5–60, $p = 0.03$). Our findings support no major role for the MDM2 SNP309 in KS development although it might influence the clinical outcome of KS in younger patients.

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Introduction

Kaposi's sarcoma (KS) is a rare tumor that occurs in four different clinico-epidemiological forms including classic, endemic, iatrogenic, and epidemic KS [1–3]. Human herpesvirus 8 (HHV-8) is shown to be the primary etiological cause of all KS forms [4, 5]. The seroprevalence rate of HHV-8 significantly varies in different geographical regions. Indeed, it is below 10% in northern Europe, North America, and most parts of Asia, from 10 to 30% in the Mediterranean area, and above 50% in sub-Saharan Africa and parts of South America. In general, the seroprevalence of HHV-8 infection is in parallel to Kaposi's sarcoma incidence [6–9].

While the seroprevalence of HHV-8 is reported to be high in some populations, only a small percentage of HHV-8-seropositive subjects progress to KS, supporting a prerequisite role of virus infection although it appears not to be sufficient for KS development. While the role of immune suppression behind KS progression is well documented, both environmental and genetic factors together with ethnic origins are likely to play a major role in this scenario [2, 10, 11].

The prevalence of HHV-8 has been reported in 2–3.6% of general population [12, 13], 16.9% of haemodialysis patients [13], 25% of renal transplant recipients [14] and 45.7% of HIV-infected patients [13]. The incidence of KS was reported to be high among Iranian renal transplant recipients (ranging from 0.45 to 2.4%) [13] although KS is a rare cancer in general population (0.06–0.17 per 100,000) [15]. The high KS incidence in renal transplant subjects

suggests that the virus might be prevalent in general population, but only a few infected people may have the chance to develop KS due to specific predisposing genetic or environmental factors.

MDM2 is a major negative regulator of p53 [16, 17] and its overexpression can inhibit the function of p53, allowing the damaged cells to escape the cell-cycle checkpoint control and finally progress to cancer [17–19]. In several human tumors, the overexpression of MDM2 protein has been shown, suggesting a main role for this protein in tumorigenesis via proteasome-mediated degradation of p53 and, consequently, inhibition of apoptosis [20, 21].

A polymorphism in the MDM2 promoter (SNP309T>G, rs2279744) has been linked to the increased binding of Sp1 transcription factor and subsequent higher MDM2 protein levels [18, 19, 22]. The MDM2 polymorphism has also been associated with the earlier onset of breast cancer in Li–Fraumeni patients, colorectal cancer, soft tissue sarcoma, cutaneous melanoma, diffuse large B-cell lymphoma, and non-small-cell lung cancer [23–27].

To investigate the association of the MDM2 SNP309 with the risk of KS, we hypothesized that MDM2 SNP309 may influence the risk of KS occurrence in Iranian patients. Using restriction fragment length polymorphism, MDM2 SNP309 was genotyped in 79 classic KS patients and 123 healthy controls.

Materials and methods

Patients and controls

Eighty-six formalin-fixed paraffin-embedded cutaneous KS biopsies were obtained from patients attending the Dermatology Department of Razi Hospital over a 14-year period (2000–2014). Seventy-nine samples from patients with classic KS were included and seven samples (three epidemic and four iatrogenic) were excluded from this study. Also, a total of 123 blood samples were obtained from healthy subjects, referring to the South Tehran Health Center. The study was approved by the local ethical committee of Tehran University of Medical Sciences and informed consent was obtained from all the study subjects.

Detection of HHV-8 genome in samples

Genomic DNA for classic KS samples was extracted according to the previously published procedures [28, 29]. Peripheral blood mononuclear cells (PBMCs) were isolated from 123 fresh whole-blood samples containing EDTA by Ficoll-Paque centrifugation (GE Healthcare, Amersham, UK) and stored at −70 °C until use. Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, GmbH, Hildelberg, Germany) according to manufacturer's instruction.

MDM2 SNP309 polymorphisms analysis

The MDM2 SNP309 analysis was carried out by PCR and restriction fragment length polymorphism (RFLP). A 174-base pairs (bp) amplicon size of the MDM2 intron 1 region, containing the MspA1I polymorphic site at nucleotide 309, was amplified with the B-MDM2-309F (5′-GGGAGTTCA GGGTAAAGG-3′) and the B-MDM2-309R (5′-GACCAG CTCAAGAGGAAA-3′) primers. PCR reactions were performed in a 50-µl reaction mixture containing 100–200 ng of DNA template, 2.5 mM $MgCl_2$, 50 µM of each dNTP, 20 pmol of each primer and 1.25 U of HotMaster™ *Taq* DNA polymerase (five Prime GmbH, Hamburg, Germany), with the following PCR thermal conditions: an initial 1-min denaturation at 94 °C, followed by 40 cycles of 55 °C for 45 s, 68 °C for 1 min, 94 °C for 30 s and a final annealing at 55 °C for 30 s with 5 min of elongation at 68 °C. Digestion of MDM2 PCR products was performed by MspA1I restriction enzyme (Promega, Madison, WI, USA) for 3 h at 37 °C, and run on a 7% polyacrylamide gel.

Statistical analysis

The observed allele frequencies of study groups were evaluated by the Hardy–Weinberg equilibrium theory. A Fisher's exact test or χ^2 test was applied to compare the proportions of MDM2 alleles between case and control groups by Epi Info 7 Statistical Analysis System Software (Centers for Disease Control and Prevention, USA). The association between MDM2 genotypes with the age of onset, gender, stage of disease and distribution at presentation of tumor was also analyzed. p values less than 0.05 were considered statistically significant.

Results

A total of 79 samples taken from cutaneous classic KS lesions (59 men and 20 women) were included in this study. The mean age of patients was 61.3 years (range 25–89) at the time of diagnosis (Table 1).

The MDM2 SNP309 allele frequencies were studied using a PCR–RFLP-based method (Fig. 1). The distribution of the MDM2 SNP309 genotypes in cases and controls are shown in Table 2. The frequencies of the MDM2 SNP309 polymorphisms were found in Hardy–Weinberg equilibrium among case ($\chi^2=3.88$; $df=1$; $p=0.05$) and control group ($\chi^2=3.5$; $df=1$; $p=0.06$). The frequency of the MDM2 SNP309 T/T, T/G and G/G alleles among 79 classic KS subjects were 31.6% ($n=25$), 58.2% ($n=46$),

Table 1 Demographic features of Kaposi's sarcoma patients and healthy controls

Characteristics	
KS patients	
n	79
Age, median (range), year	61.3 (25–89)
Sex, *n* (%)	
Male	59
Female	20
Healthy subjects	
n	123
Age, median (range), year	60.1 (26–88)
Sex, *n* (%)	
Male	100
Female	23

and 10.2% ($n=8$), respectively. The corresponding figures among 123 healthy controls were also 26.9% ($n=33$), 57.7% ($n=71$) and 15.4% ($n=19$). Crude odds ratios (OR) and 95% confidence intervals (CI) were used to assess the association between the MDM2 SNP309 genotypes and the risk of KS (Table 2). Regardless of being recessive and dominant models, no significant association was found between increased KS risk and the MDM2 SNP309 genotypes (OR 1.6, 95% CI 0.67–3.9 and OR 0.79, 95% CI 0.42–1.5, respectively).

Stratification of classic KS cases was performed according to the age of onset, gender, and distribution at tumor presentation (Table 3). A statistically significant difference was found between the age of KS onset and GG genotype (odds ratio 9.5, 95% Confidence Intervals 1.5–60, $p=0.03$). Indeed, an average age of KS onset was at 47.5 years for GG allele compared to 63.2 years for TT alleles. However, the association found between the gender and distribution at presentation with MDM2 SNP309 genotypes was not statistically significant. These results suggest that the G allele might be associated to the KS development in young people.

Discussion

While some epidemiological studies have evaluated the association of MDM2 SNP309 polymorphism and

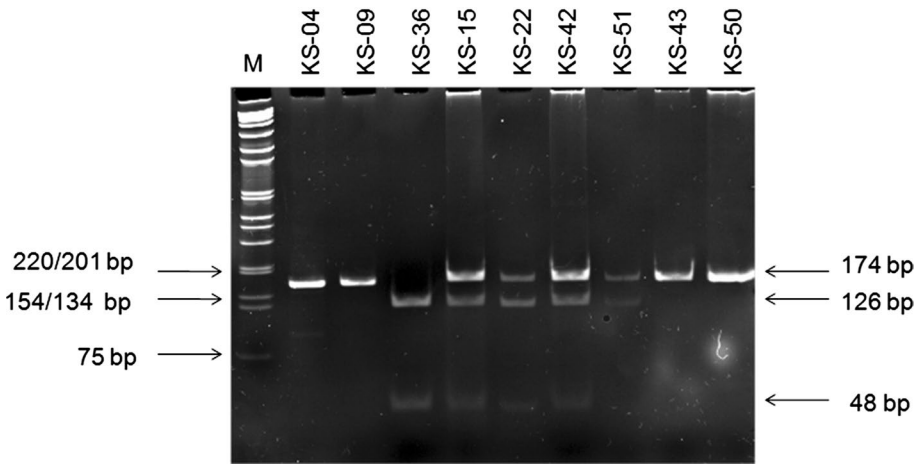

Fig. 1 The polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) result of MDM2 SNP309. MDM2 SNP309 T allele was not cleaved by MspAI endonuclease and had a single band of 174 bp. The MDM2 SNP309 G allele was cleaved by MspAI and had two small bands of 126 and 48 bp. The MDM2 SNP309 heterozygote had three fragments of 174, 126 and 48 bp

Table 2 Distribution of MDM2 SNP309 variants in classic Kaposi's sarcoma cases and controls

	KS patients ($n=79$) *n* (%)	Controls ($n=123$) *n* (%)	OR [95% CI]	*p* Value
Genotype				
T/T	25 (31.6)	33 (26.9)	1	
T/G	46 (58.2)	71 (57.7)	0.85 (0.45–1.6)	0.75
G/G	8 (10.2)	19 (15.4)	0.55 (0.2–1.4)	0.34
Recessive model				
T/T + T/G	71 (89.8)	104 (84.5)	1	
G/G	8 (10.2)	19 (15.4)	1.6 (0.67–3.9)	0.38
Dominant model				
T/T	25 (31.6)	33 (26.9)	1	
T/G + G/G	54 (68.4)	90 (73.2)	0.79 (0.42–1.5)	0.56

Table 3 Association of MDM2 SNP309 with demographic and clinicopathologic features of Kaposi's sarcoma

MDM2 SNP309	The age of KS onset		OR [95% CI]	*p* value
	≤50 (*n* = 23) *n* (%)	>50 (*n* = 56) *n* (%)		
TT	6 (26.1)	19 (33.9)	1	
TG	11 (47.8)	35 (62.5)	0.99 (0.3–3.1)	0.77
GG	6 (26.1)	2 (3.6)	9.5 (1.5–60)	0.03
	Gender		OR [95% CI]	*p* value
	Male (*n* = 59) *n* (%)	Female (*n* = 20) *n* (%)		
TT	17 (28.8)	8 (40)	1	
TG	34 (57.6)	12 (60)	0.75 (0.26–2.2)	0.8
GG	8 (13.6)	0 (0)	–	0.156
	Distribution at presentation		OR [95% CI]	*p* value
	Local (*n* = 45) *n* (%)	Disseminated (*n* = 34) *n* (%)		
TT	17 (37.8)	8 (23.5)	1	
TG	23 (51.1)	23 (67.6)	0.47 (0.17–1.3)	0.23
GG	5 (11.1)	3 (8.9)	0.78 (0.15–4.1)	0.99

risk of several cancers [18, 19, 30–36], only one study has evaluated the association of the MDM2 SNP309 polymorphism in KS patients [37]. In the present study, the MDM2 nucleotide 309 polymorphism was investigated in 79 classic KS cases and 123 healthy controls to investigate the impact of these alleles on the risk of KS development. Although this study supports no association between genetic polymorphisms in MDM2 and the KS risk, an association was found between the increased frequency of the MDM2 SNP309 G/G genotype and younger age of KS patients.

While the correlation between MDM2 SNP309 and different types of malignancies has been studied in previous studies, the results were shown to be inconsistent [18, 22, 38–41]. Our results are in line with the previous studies reporting no correlation between MDM2 SNP309 and some types of cancers [32, 38–40]. In this regard, Wilkening et al. (2007) performed a combined analysis on breast, colorectal, and lung cancers to assess the consistency of the associations for the MDM2 SNP309 G allele. The results obtained from this study indicate no impact for MDM2 SNP309 alleles and the risk of breast or colorectal cancers (OR = 0.97, 95% CI = 0.87–1.08 and OR = 0.97, 95% CI = 0.76–1.25), respectively [41]. However, the combined estimation of the ORs showed a higher risk for GG opposed to TT (OR = 1.27, 95% CI = 1.12–1.44) in lung cancer. The data also revealed that MDM2 SNP309 has slight or no impact on the risk of several cancers although it might have an effect on the time of tumor onset and prognosis [41].

The potential role of the MDM2 SNP309 polymorphism in KS progression has been investigated in few geographical regions in the world [37]. In Africa, MDM2 SNP309 G genotype has not been associated with the risk of KS [37]. However, in Caucasian KS patients, MDM2 SNP309 G genotype has been associated with the increased risk of KS (OR 1.99, 95% CI 0.95–4.2) [37].

It should be considered that HHV-8 has evolved its own strategies to manipulate and inhibit the p53 activity. HHV-8 expresses several viral proteins that inhibit p53 functions at several levels and thereby mediate viral oncogenesis: (1) the latency-associated nuclear antigen (LANA) binds to both p53 and MDM2, thereby inhibiting the ability of p53 to induce cell death [42, 43]. LANA interacts with the p53 and represses its transcriptional activity [42]. (2) the viral interferon regulatory factors 1, 3 and 4 interfere with p53 signaling through different mechanisms [44]. vIRF1 and vIRF3 directed ubiquitination and proteasome-mediated degradation of p53 [45, 46]. vIRF3 also antagonizes p53 oligomerization and the DNA-binding affinity due to inhibition of p53 phosphorylation [45]. vIRF4 led to decrease in total p53 levels, due to interaction with and stabilization of MDM2 [47].

According to the age of KS onset, the G allele tended to have an increased risk at a young age, suggesting that the G allele might be associated with susceptibility to KS risk in younger age. To support this view, an association between the G allele and increased risk at a young age has been observed for cutaneous melanoma, soft tissue

sarcomas, breast cancer, and renal cell carcinoma [26, 27, 48, 49]. In a study conducted on sporadic soft tissue sarcomas, the average age of onset was 45 years and 57 years for those patients who had the G/G and T/T genotype, respectively [48]. It has also been shown that the G allele of SNP309 increases the basal level of MDM2 in cells, as a result of the creation of an enhanced SP1 transcription factor-binding site in the MDM2 promoter. The higher levels of MDM2 in cells diminish the p53 apoptotic responses. The lower frequency of cells undergoing apoptosis and the propagation of mutated cells in individuals harboring G/G genotype at SNP30 of MDM2 have been suggested to permit cancers to arise at younger ages over a lifetime [48].

In agreement with some previous studies showing no association between the MDM2 alleles and gender or distribution at presentation in cutaneous melanoma, lung cancer and pancreatic cancer, we found no association between the gender and stage of disease [26, 50, 51].

While modest sample size of the KS cases can be considered as a limiting factor in the present study, by matching on age and sex in both, we have tried to minimize the potential confounding factors.

In conclusion, our findings partially support no association between the MDM2 SNP309 genotypes and the risk of KS development. An explanation of this finding is the fact that other genes and SNPs can modify the MDM2 SNP309 GG phenotype and enhance p53 function in a cell. Although MDM2 SNP309 is not a risk factor in KS development, it might influence the age of classic KS onset. To confirm the role of MDM2 polymorphism in KS development, the findings further need to be verified in large studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval The study was approved by the Ethical Committee of Tehran University of Medical Sciences (Grant No. 17715).

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