J Cancer Res Clin Oncol (2012) 138:555–561
DOI 10.1007/s00432-011-1124-8

ORIGINAL PAPER

The functional MDM2 T309G genetic variant but not P53 Arg72Pro polymorphism is associated with risk of sarcomas: a meta-analysis

Xu Cai · Ming Yang

Received: 5 October 2011 / Accepted: 9 December 2011 / Published online: 29 December 2011

Abstract
Purpose The P53–MDM2 pathway plays a central role in sarcoma pathogenesis. Functional P53 Arg72Pro and MDM2 T309G single-nucleotide polymorphisms (SNP) are considered to have significant effects on risk of sarcomas.
Methods Several molecular epidemiology studies have evaluated how these genetic variants are involved in sarcoma development, but the conclusions are inconsistent. Therefore, we conducted this meta-analysis to systematically examine the association between these functional SNPs and sarcoma risk.
Results There are four studies eligible for P53 Arg72Pro SNP (466 sarcoma patients and 552 controls), and three studies for MDM2 T309G SNP (355 sarcoma patients and 645 controls). Pooled odds ratios were appropriately calculated using either fixed-effect model or random-effect model. We did not find a significant association between P53 Arg72Pro polymorphism and sarcoma risk. However, in a stratified analysis, a statistically significant correlation between this SNP and osteosarcoma risk was observed. For MDM2 T309G variant, pooled results from the meta-analysis indicate that carriers of TG and GG genotypes showed a 34% increased risk to develop sarcomas compared to TT carriers.
Conclusion These results suggest that the functional MDM2 T309G genetic variant may play a more important role in carcinogenesis of sarcoma.

X. Cai
Department of Orthopedics, Division of Surgery, Chinese PLA General Hospital, Beijing, China

M. Yang (✉)
College of Life Science and Technology, Beijing University of Chemical Technology, P. O. Box 53, Beijing 100029, China
e-mail: yangm@mail.buct.edu.cn

Keywords P53 · MDM2 · Single-nucleotide polymorphism · Sarcoma · Osteosarcoma

Introduction

There are a set of complex systems that could protect cells against the genotoxic insults and maintain integrity of human genome. Among all these systems, the P53 tumor suppressor pathway plays an essential role in the cellular response to stress by inducing cell growth arrest or apoptosis (Meek 2009; Vogelstein et al. 2000). High frequencies of P53 mutations have been found in many types of human cancer, including sarcomas, and are also correlated to the process of carcinogenesis (Cheok et al. 2011). Both mice and humans harboring germ line-inactivating mutations in one P53 allele are highly susceptible to sarcomas (Malkin et al. 1990). Moreover, genetic polymorphisms in P53 may also be associated with an increased risk of developing certain cancers (Yang et al. 2007; Hong et al. 2005).

MDM2, a key regulator of P53 tumor suppressor pathway, can directly bind to P53 protein, inhibit its activity, and lead to its degradation via the ubiquitination pathway. P53 could also activate MDM2 transcription and increase MDM2 expression (Landers et al. 1997; Chen et al. 1996). It has been shown that sarcomas overexpress MDM2 and, in some cases, have amplification of MDM2 gene locus without P53 mutation (Flørenes et al. 1994; Leach et al. 1993). These results indicate that MDM2 overexpression may take the place of inactivating P53 mutations in cancer development.

A MDM2 single-nucleotide polymorphism (SNP) (T309G) (rs2279744), which is in the promoter region of MDM2, can increase affinity for stimulatory protein (Sp) 1 binding and result in increased MDM2 expression and the

subsequent attenuation of the P53 pathway (Bond et al. 2004). It has been found that this SNP is associated with susceptibility to sarcomas and many other cancers (Yang et al. 2007; Hong et al. 2005; Bond et al. 2005; Bond and Levine 2007). Moreover, there is also a functional P53 polymorphism, the G>C change at codon 72 (rs1042522), which results in Arg>Pro amino acid substitution. It has been shown that 72Arg allele may induce apoptosis with faster kinetics than the 72Pro allele (Dumont et al. 2003; Bergamaschi et al. 2006). On the other hand, the 72Pro variant seems to be more competent in inducing cell cycle arrest and DNA repair (Siddique and Sabapathy 2006; Ørsted et al. 2007).

Sarcomas include tumors of bone, cartilage, fat, muscle, vascular, and hematopoietic tissues, such as osteosarcoma, liposarcoma, leiomyosarcoma, and Kaposi's sarcoma. Osteosarcoma is the most common primary bone malignancy and frequently found in adolescents and young adults (Ottaviani and Jaffe 2009; Mirabello et al. 2009). It is rarely diagnosed before the age of five, but the incidence increases with age until around puberty (Ottaviani and Jaffe 2009; Mirabello et al. 2009). Rates of childhood and adolescent osteosarcoma are relatively consistent worldwide, ranging between 3 and 4.5 cases/million population/year (Ottaviani and Jaffe 2009; Mirabello et al. 2009). Osteosarcoma has been well characterized as one of the tumors known to occur in Li-Fraumeni syndrome, the cancer predisposition syndrome resulting from germ line mutations in P53 (Palmero et al. 2010). In addition, frequent gene amplification of MDM2 was observed in osteosarcoma tissues (Wunder et al. 1999), indicating that p53–MDM2 pathway plays an important role in osteosarcoma development.

Soft tissue sarcomas are an exceptionally heterogeneous group of uncommon tumors constituting less than 1% of all malignant tumors and consist of more than 50 histopathologic types and subtypes (Vesely et al. 2009). Soft tissue sarcomas include sarcomas arising from the nonepithelial extraskeletal tissue of mesenchymal origin and most commonly localize in the deep soft parts of the limb or limb girdle but also the subcutaneous tissue, trunk wall, head and neck, and retroperitoneal, intraabdominal, and pelvic areas (Clark et al. 2005). They are responsible for about 1% of all adult malignancies (Clark et al. 2005), and their management is an important medical challenge. Among soft tissue sarcomas, leiomyosarcoma is a relatively rare form and comprising ~5–10% of soft tissue sarcomas (Kotilingam et al. 2006). Genetic factors play an essential role in the development of soft tissue sarcomas, including translocations and mutations in tumor suppressor genes and oncogenes (Kotilingam et al. 2006).

There are four epidemiological forms of Kaposi's sarcoma (Gallo 1998): (1) classic Kaposi's sarcoma; (2) endemic Kaposi's sarcoma (Oettle 1962; Slavin et al. 1970; Bhagwat et al. 1980); (3) iatrogenic Kaposi's sarcoma (Siegel et al. 1969); (4) epidemic or AIDS-Kaposi's sarcoma. The human herpesvirus type 8 (HHV-8), which was the firstly isolated in AIDS-associated Kaposi's sarcoma, has been identified in virtually 100% of tumor biopsies and defined as the etiological agent of all forms of Kaposi's sarcoma (Chang et al. 1994; Buonaguro et al. 1996). Interestingly, the HHV-8 virus interferes with the P53–MDM2 pathway through several ways, such as suppression of P53 transcription and transactivation activity by HHV-8 latency-associated nuclear antigen (LANA) (Friborg et al. 1999; Si and Robertson 2006), and specifically interaction with MDM2 and stabilization of MDM2 by the viral interferon regulatory factor 4 (vIRF4) (Rayburn et al. 2005; Lee et al. 2009). These results indicate the importance of the P53–MDM2 pathway during oncogenesis of Kaposi's sarcoma.

Considering the central role of P53–MDM2 pathway in the response to DNA damage and preventing sarcoma pathogenesis, we hypothesized that functional P53 Arg72Pro and MDM2 T309G polymorphisms might be genetic susceptibility factors for the development of sarcomas. To test this hypothesis, we systematically analyzed the differential role of P53 and MDM2 variants on carcinogenesis of sarcomas through a meta-analysis.

Materials and methods

Literature search and data extraction

HuGE Navigator (version 2.0) (HuGE Literature Finder 2011; Yu et al. 2008) and PubMed (US National Library of Medicine, National Institutes of Health 2011) were used for the electronic literature searches with search terms of "P53," "TP53," "MDM2," "HDM2," "sarcoma," "polymorphism," "SNP," as well as their combinations. Case–control studies of P53 Arg72Pro or MDM2 T309G polymorphism published from November 2004 to July 2011 were identified without language restrictions. We also identified additional studies by screening reference lists of key studies and reviews. Selection criteria of an eligible study included: (a) original studies; (b) studies that investigated the association between the P53 Arg72Pro or MDM2 T309G polymorphism and risk of sarcomas; and (c) studies that reported crude odds ratio (OR) with 95% confidence interval (CI) values or sufficient data to calculate crude OR and 95% CI. The raw data and demographic information, including first author, published year, original country, ethnicity, sample size, cancer types, and genotypes, were independently extracted by two investigators (Yang M. and Cai X.) and reached conformity on all items through consultation.

Statistical analysis

Association between P53 Arg72Pro or MDM2 T309G polymorphism and cancer risk was re-calculated using crude ORs together with their corresponding 95% CIs. The combined ORs were performed for the models of Arg/Arg versus Arg/Pro + Pro/Pro (P53 Arg72Pro) or TT versus TG + GG (MDM2 T309G). Further analysis was done by subgrouping studies into osteosarcoma, soft tissue sarcoma (including uterine leiomyosarcoma), or Kaposi's sarcoma based on their general populations. If the *P* value of the heterogeneity test was $\geq$0.05, a fixed-effect model (the Mantel–Haenszel method) was performed to calculate the combined OR (Mantel and Haenszel 1959), which assumed the same homogeneity of effect size across all studies. If the *P* value of the heterogeneity test was <0.05, it showed that the between-study heterogeneity was statistically significant. A random-effects mode (the DerSimonian and Laird method) was used to calculate the combined OR (Petitti 1994). Publication bias was tested graphically by using funnels plots, in which the standard error was plotted against the log(OR) to form a simple scatter plot, and the funnel plot asymmetry was assessed by the method of Egger's test (Egger et al. 1997). Asymmetric plots could indicate potential existing publication bias. The statistical analyses were performed using Stata Statistical package (version 11.0; Stata Corp., College Station, TX), Review Manager (Version 4.2, the Cochrane Collaboration), and Statistical Analysis System (version 9.0; SAS Institute, Cary, NC). All *P* values were two-sided.

Results

Literature search and data extraction

We searched HuGE Navigator and NCBI PubMed using the keywords "P53," "TP53," "sarcoma," "polymorphism," or "SNP" and found 29 studies. Of these 29 studies, 25 studies were excluded either because they were not case–control studies or they are not studies on sarcomas or reports on the role of P53 Arg72Pro on patient survival or disease progression. Among these four case–control studies, Savage et al. (2007) and Toffoli et al. (2009) investigated role of P53 Arg72Pro in osteosarcoma development among Caucasians, and the other two studies examined effects of this SNP on carcinogenesis of soft tissue sarcomas or Kaposi's sarcoma in mixed populations (Almeida et al. 2008; Tornesello et al. 2009). In addition, after searching HuGE Navigator and NCBI PubMed using the keywords "MDM2," "HDM2," "sarcoma," "polymorphism," or "SNP," we found 13 studies. Of these 13 studies, 10 studies were excluded because either they were not case–control studies or they are not studies on sarcomas or reports on the role of MDM2 T309G on patient survival or disease progression. Among these three reports, Alhopuro et al. (2005) studied association between MDM2 SNP and risk of uterine leiomyosarcoma in Finish, Toffoli et al. (2009) examined effect of this polymorphism on osteosarcoma in Caucasians, and Tornesello et al. (2011) evaluated the role of this polymorphism in Kaposi's sarcoma among Africans and Caucasians. A database, including information extracted from each article, was created. Table 1 showed the essential information, including SNPs genotyped, first author, year of publication, sample size, country, ethnicity, and cancer types.

Quantitative data synthesis

For the P53 Arg72Pro polymorphism, we obtained our meta-analysis data from 4 datasets consisting of 466 sarcoma patients and 552 controls. Since the between-study heterogeneity was observed, the association between the P53 Arg72Pro genotype and sarcoma risk was estimated using random-effect model. Compared with Arg/Arg genotype, the carriers of Arg/Pro and Pro/Pro genotypes showed a decreased risk to develop sarcomas (OR = 0.76, 95% CI = 0.44–1.30) (Fig. 1). However, the association was not statistically significant ($P > 0.05$). For osteosarcoma, there were two studies including 299 cases and 317 controls, and no between-study heterogeneity was found (*Q* test, $P = 0.17$). In fixed-effect model, a statistically significant correlation between the P53 polymorphism and osteosarcoma risk was observed with the OR of 0.53 (95% CI = 0.36–0.78, $P < 0.05$). The effects of the MDM2 T309G polymorphism were also evaluated in 355 sarcoma patients and 645 controls. Compared with TT genotype, a 1.34-fold increased risk to develop sarcomas was observed in individuals with TG and GG genotypes in a fixed-effect model (95% CI = 1.02–1.76, $P < 0.05$) (Fig. 2).

Bias diagnostics

For publication bias evaluation, genotypes of P53 Arg72Pro and MDM2 T309G polymorphisms were plotted against the precision ones using a funnel plot. The result was approximately symmetrical, and no publication bias in the current meta-analysis was observed (Egger's test: $P = 0.822$ for P53 Arg72Pro; $P = 0.578$ for MDM2 T309G). This indicates that biases from publications and other factors may not have a significant influence on the results of our meta-analysis of association between P53 Arg72Pro or MDM2 T309G polymorphism and sarcoma risk (Fig. 3).

Table 1 Studies included in the meta-analyses of association between P53 Arg72Pro or MDM2 T309G SNP and sarcomas

SNP	Source	Case no.	Control no.	Country	Ethnicity	Cancer types
P53 Arg72Pro	Savage et al. (2007)	98	68	USA	Caucasian	Osteosarcoma
	Almeida et al. (2008)	100	85	Brazil	Mixed	Soft tissue sarcomas
	Toffoli et al. (2009)	201	250	Italy	Caucasian	Osteosarcoma
	Tornesello et al. (2009)	67	150	Cameroon, Kenya, Uganda, Italy, Greece, and USA	African and Caucasian	Kaposi's sarcoma
MDM2 T309G	Alhopuro et al. (2005)	68	185	Finland	Finish	Uterine leiomyosarcoma
	Toffoli et al. (2009)	201	250	Italy	Caucasian	Osteosarcoma
	Tornesello et al. (2011)	86	210	Cameroon, Kenya, Uganda, Italy, Greece, and USA	African and Caucasian	Kaposi's sarcoma

SNP, single-nucleotide polymorphism

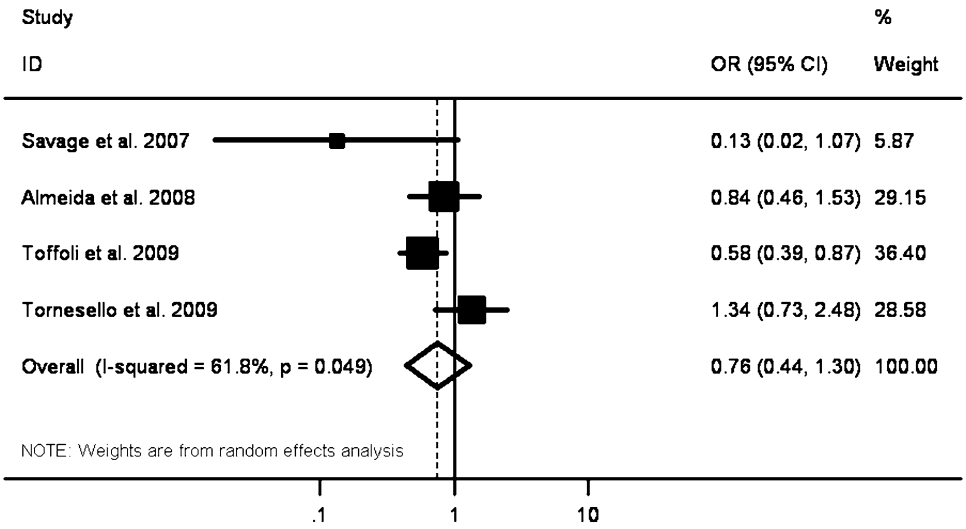

Fig. 1 Meta-analysis for P53 Arg72Pro polymorphism (Arg/Arg vs. Arg/Pro + Pro/Pro) in sarcomas

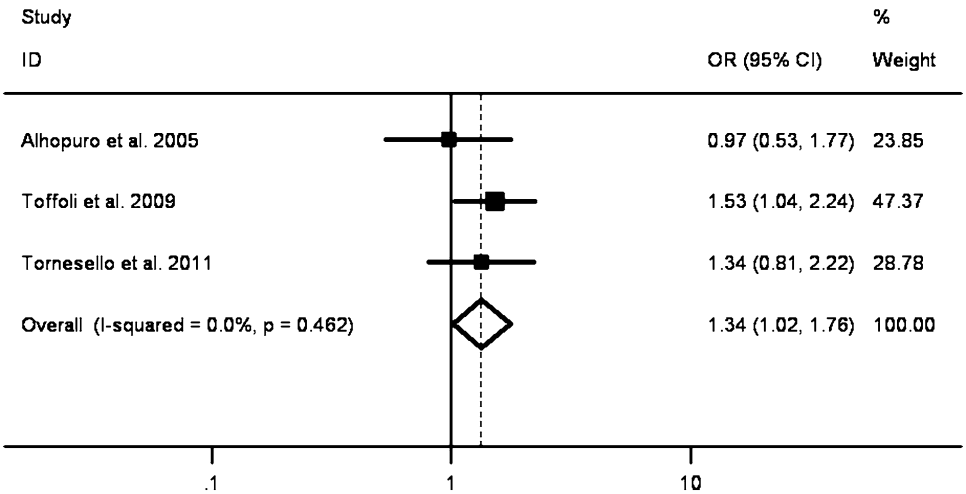

Fig. 2 Meta-analysis for MDM2 T309G polymorphism (TT vs. TG + GG) in sarcomas

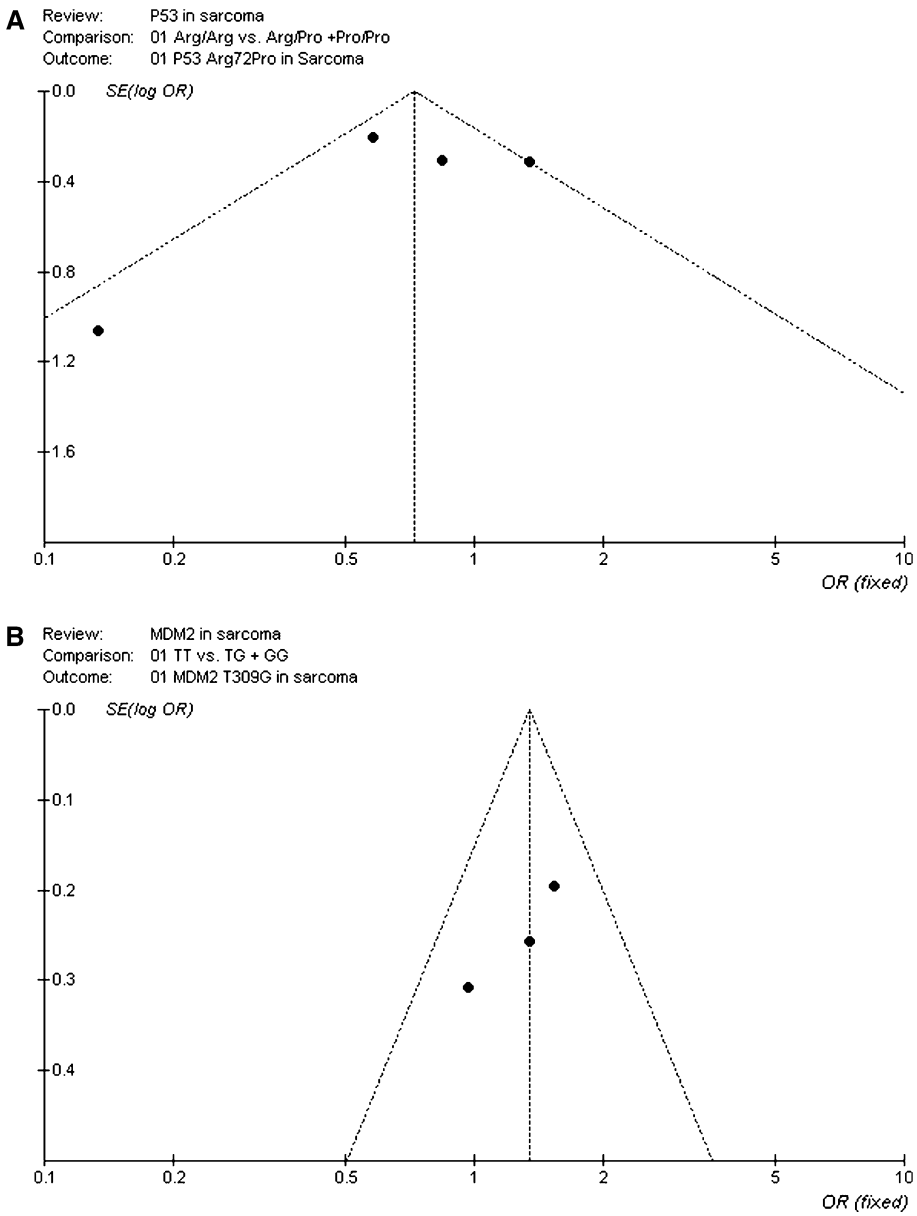

Fig. 3 Funnel plots of the Egger's test of allele comparison for publication bias. **a** Funnel plot for P53 Arg72Pro Arg/Arg versus Arg/Pro + Pro/Pro comparison in sarcomas; **b** funnel plot for MDM2 T309G TT versus TG + GG comparison in sarcomas. No asymmetry was found as indicated by the *P* value of Egger's test

Discussion

It has been shown that attenuated P53–MDM2 pathway resulting from germ line polymorphisms is associated with increased risk of carcinogenesis (Yang et al. 2007; Hong et al. 2005; Bond et al. 2005; Bond and Levine 2007). To summarize the role of P53 Arg72Pro or MDM2 T309G polymorphism in carcinogenesis of sarcomas, a meta-analysis including six published studies was done. It was found that P53 Arg72Pro SNP is not associated with the development of sarcomas in general but is associated with the development of osteosarcoma. However, significant association between MDM2 T309G polymorphism and sarcoma development could be observed.

Acting as a tumor suppressor, P53 could lead to cell growth arrest and/or apoptosis in response to DNA damage and other cellular stresses (Meek 2009; Vogelstein et al. 2000). The p53 function is controlled by MDM2, which binds to P53 and prevents P53-dependent cell cycle arrest or apoptosis (Arva et al. 2005; Haupt et al. 1997). On the other hand, the MDM2 promoter is regulated by P53 (Barak et al. 1993). The functional P53 Arg72Pro polymorphism has been shown to depress the activities of P53 in inducing apoptosis, cell cycle arrest, and DNA repair (Dumont et al. 2003; Bergamaschi et al. 2006; Siddique and Sabapathy 2006; Ørsted et al. 2007). In the current meta-analysis, we did not find significant association between P53 Arg72Pro and risk of sarcomas. However, in a stratified analysis, a significantly reduced risk of individuals carrying Arg/Pro and Pro/Pro to develop osteosarcoma was observed. This observation is not a surprise because the 72Pro allele could induce cell cycle arrest and DNA

repair more efficiently to prevent transformation of normal cells (Siddique and Sabapathy 2006; Ørsted et al. 2007). Probably, in osteosarcoma, the 72Pro allele plays a dominant role in oncogenesis compared to the 72Arg allele, which can induce apoptosis with faster kinetics.

MDM2 is considered to be an oncogene, and its overexpression has been correlated to carcinogenesis and cancer progression (Eymin et al. 2002; Polsky et al. 2001). We and other groups observed positive association between MDM2 T309G polymorphism and several cancers, including sarcomas (Yang et al. 2007; Hong et al. 2005; Bond et al. 2005; Bond and Levine 2007; Alhopuro et al. 2005; Toffoli et al. 2009; Tornesello et al. 2011). Consistent to our previous observation in gastric cardia adenocarcinoma, this meta-analysis demonstrated that individuals with G allele, which is related to elevated MDM2 expression and MDM2 amplification (Ito et al. 2011), showed significantly increased risk to develop sarcomas. The different results between P53 Arg72Pro and MDM2 T309G SNPs may be due to different genetic components of P53 and MDM2 genes in sarcoma development. For P53 gene, mutations (including K132R, K164N[het], V173L[het], D186splice, Y205stop, D208G [het], A221fs, M237I, 2 S241fs[het], C242F, G244S[het], R248G, E258fs[het], R267W, G279E, R282fs[het], E285K, E286K, R290C[het], and R337L) might contribute more to cell transformation compared to the P53 Arg72Pro polymorphism (Ito et al. 2011). However, MDM2 amplification and increased MDM2 expression might be more important susceptible factors for sarcomas (Ito et al. 2011). Interestingly, MDM2 G allele is strongly associated with elevated MDM2 expression and MDM2 amplification. This functional relevance of MDM2 polymorphism is consistent with the molecular epidemiological finding, demonstrating that the G allele is a risk allele for sarcomas.

In summary, our study shows that the functional MDM2 T309G SNP but not P53 Arg72Pro variant is associated with risk of sarcomas. However, P53 Arg72Pro polymorphism may play a part in development of osteosarcoma, one major type of sarcomas.

Acknowledgments This work was supported by Beijing Nova Program (no. 2010B013 to M. Yang) and the Fundamental Research Funds for the Central Universities (no. ZZ1234 to M. Yang).

Conflict of interest The authors declare no competing financial interests.

References

Alhopuro P, Ylisaukko-Oja SK, Koskinen WJ, Bono P, Arola J, Järvinen HJ, Mecklin JP, Atula T, Kontio R, Mäkitie AA, Suominen S, Leivo I, Vahteristo P, Aaltonen LM, Aaltonen LA (2005) The MDM2 promoter polymorphism SNP309T–>G and the risk of uterine leiomyosarcoma, colorectal cancer, and squamous cell carcinoma of the head and neck. J Med Genet 42:694–698

Almeida PS, Manoel WJ, Reis AA, Silva ER, Martins E, Paiva MV, Fraga AC Jr, Saddi VA (2008) TP53 codon 72 polymorphism in adult soft tissue sarcomas. Genet Mol Res 7:1344–1352

Arva NC, Gopen TR, Talbott KE, Campbell LE, Chicas A, White DE, Bond GL, Levine AJ, Bargonetti J (2005) A chromatin-associated and transcriptionally inactive p53-Mdm2 complex occurs in mdm2 SNP309 homozygous cells. J Biol Chem 280:26776–26787

Barak Y, Juven T, Haffner R, Oren M (1993) mdm2 expression is induced by wild type p53 activity. EMBO J 12:461–468

Bergamaschi D, Samuels Y, Sullivan A, Zvelebil M, Breyssens H, Bisso A, Del Sal G, Syed N, Smith P, Gasco M, Crook T, Lu X (2006) iASPP preferentially binds p53 proline-rich region and modulates apoptotic function of codon 72-polymorphic p53. Nat Genet 38:1133–1141

Bhagwat GP, Naik KG, Sachdeva R, Bhushan V (1980) Disseminated lymphadenopathic Kaposi's sarcoma in Zambian children. Med J Zambia 14:61–63

Bond GL, Levine AJ (2007) A single nucleotide polymorphism in the p53 pathway interacts with gender, environmental stresses and tumor genetics to influence cancer in humans. Oncogene 26:1317–1323

Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, Bargonetti J, Bartel F, Taubert H, Wuerl P, Onel K, Yip L, Hwang SJ, Strong LC, Lozano G, Levine AJ (2004) A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 119:591–602

Bond GL, Hu W, Levine A (2005) A single nucleotide polymorphism in the MDM2 gene: from a molecular and cellular explanation to clinical effect. Cancer Res 65:5481–5484

Buonaguro FM, Tornesello ML, Beth-Giraldo E, Hatzakis A, Mueller N, Downing R, Biryamwaho B, Sempala SD, Giraldo G (1996) Herpesvirus-like DNA sequences detected in endemic, classic, iatrogenic and epidemic Kaposi's sarcoma (KS) biopsies. Int J Cancer 65:25–28

Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869

Chen J, Wu X, Lin J, Levine AJ (1996) mdm-2 inhibits the G1 arrest and apoptosis functions of the p53 tumor suppressor protein. Mol Cell Biol 16:2445–2452

Cheok CF, Verma CS, Baselga J, Lane DP (2011) Translating p53 into the clinic. Nat Rev Clin Oncol 8:25–37

Clark MA, Fisher C, Judson I, Thomas JM (2005) Soft-tissue sarcomas in adults. N Engl J Med 353:701–711

Dumont P, Leu JI, Della Pietra AC 3rd, George DL, Murphy M (2003) The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 33:357–365

Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634

Eymin B, Gazzeri S, Brambilla C, Brambilla E (2002) Mdm2 overexpression and p14(ARF) inactivation are two mutually exclusive events in primary human lung tumors. Oncogene 21:2750–2761

Flørenes VA, Maelandsmo GM, Forus A, Andreassen A, Myklebost O, Fodstad O (1994) MDM2 gene amplification and transcript levels in human sarcomas: relationship to TP53 gene status. J Natl Cancer Inst 86:1297–1302

Friborg J Jr, Kong W, Hottiger MO, Nabel GJ (1999) p53 inhibition by the LANA protein of KSHV protects against cell death. Nature 402:889–894

Gallo RC (1998) The enigmas of Kaposi's sarcoma. Science 282:1837–1839

Haupt Y, Maya R, Kazaz A, Oren M (1997) Mdm2 promotes the rapid degradation of p53. Nature 387:296–299

Hong Y, Miao X, Zhang X, Ding F, Luo A, Guo Y, Tan W, Liu Z, Lin D (2005) The role of P53 and MDM2 polymorphisms in the risk of esophageal squamous cell carcinoma. Cancer Res 65:9582–9587

HuGE Literature Finder (2011). http://hugenavigator.net/HuGENavigator/startPagePubLit.do

Ito M, Barys L, O'Reilly T, Young S, Gorbatcheva B, Monahan J, Zumstein-Mecker S, Choong PF, Dickinson I, Crowe P, Hemmings C, Desai J, Thomas DM, Lisztwan J (2011) Comprehensive mapping of p53 pathway alterations reveals an apparent role for both SNP309 and MDM2 amplification in sarcomagenesis. Clin Cancer Res 17:416–426

Kotilingam D, Lev DC, Lazar AJ, Pollock RE (2006) Staging soft tissue sarcoma: evolution and change. CA Cancer J Clin 56:282–291 quiz 314–315

Landers JE, Cassel SL, George DL (1997) Translational enhancement of mdm2 oncogene expression in human tumor cells containing a stabilized wild-type p53 protein. Cancer Res 57:3562–3568

Leach FS, Tokino T, Meltzer P, Burrell M, Oliner JD, Smith S, Hill DE, Sidransky D, Kinzler KW, Vogelstein B (1993) p53 Mutation and MDM2 amplification in human soft tissue sarcomas. Cancer Res 53:2231–2234

Lee HR, Toth Z, Shin YC, Lee JS, Chang H, Gu W, Oh TK, Kim MH, Jung JU (2009) Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor 4 targets MDM2 to deregulate the p53 tumor suppressor pathway. J Virol 83:6739–6747

Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, Friend SH (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233–1238

Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748

Meek DW (2009) Tumour suppression by p53: a role for the DNA damage response? Nat Rev Cancer 9:714–723

Mirabello L, Troisi RJ, Savage SA (2009) Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 115:1531–1543

Oettle AG (1962) Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes. Acta Unio Int Contra Cancrum 18:330–363

Ørsted DD, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG (2007) Tumor suppressor p53 Arg72Pro polymorphism and longevity, cancer survival, and risk of cancer in the general population. J Exp Med 204:1295–1301

Ottaviani G, Jaffe N (2009) The epidemiology of osteosarcoma. Cancer Treat Res 152:3–13

Palmero EI, Achatz MI, Ashton-Prolla P, Olivier M, Hainaut P (2010) Tumor protein 53 mutations and inherited cancer: beyond Li-Fraumeni syndrome. Curr Opin Oncol 22:64–69

Petitti DB (1994) Of babies and bathwater. Am J Epidemiol 140:779–782

Polsky D, Bastian BC, Hazan C, Melzer K, Pack J, Houghton A, Busam K, Cordon-Cardo C, Osman I (2001) HDM2 protein overexpression, but not gene amplification, is related to tumorigenesis of cutaneous melanoma. Cancer Res 61:7642–7646

Rayburn E, Zhang R, He J, Wang H (2005) MDM2 and human malignancies: expression, clinical pathology, prognostic markers, and implications for chemotherapy. Curr Cancer Drug Targets 5:27–41

Savage SA, Burdett L, Troisi R, Douglass C, Hoover RN, Chanock SJ, National Osteosarcoma Etiology study group (2007) Germline genetic variation of TP53 in osteosarcoma. Pediatr Blood Cancer 49:28–33

Si H, Robertson ES (2006) Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen induces chromosomal instability through inhibition of p53 function. J Virol 80:697–709

Siddique M, Sabapathy K (2006) Trp53-dependent DNA-repair is affected by the codon 72 polymorphism. Oncogene 25:3489–3500

Siegel JH, Janis R, Alper JC, Schutte H, Robbins L, Blaufox MD (1969) Disseminated visceral Kaposi's sarcoma. Appearance after human renal homograft operation. JAMA 207:1493–1496

Slavin G, Cameron HM, Forbes C, Mitchell RM (1970) Kaposi's sarcoma in East African children: a report of 51 cases. J Pathol 100:187–199

Toffoli G, Biason P, Russo A, De Mattia E, Cecchin E, Hattinger CM, Pasello M, Alberghini M, Ferrari C, Scotlandi K, Picci P, Serra M (2009) Effect of TP53 Arg72Pro and MDM2 SNP309 polymorphisms on the risk of high-grade osteosarcoma development and survival. Clin Cancer Res 15:3550–3556

Tornesello ML, Biryahwaho B, Downing R, Hatzakis A, Alessi E, Cusini M, Ruocco V, Katongole-Mbidde E, Buonaguro L, Buonaguro FM (2009) TP53 codon 72 polymorphism in classic, endemic and epidemic Kaposi's sarcoma in African and Caucasian patients. Oncology 77:328–334

Tornesello ML, Buonaguro L, Cristillo M, Biryahwaho B, Downing R, Hatzakis A, Alessi E, Cusini M, Ruocco V, Viviano E, Romano N, Katongole-Mbidde E, Buonaguro FM (2011) MDM2 and CDKN1A gene polymorphisms and risk of Kaposi's sarcoma in African and Caucasian patients. Biomarkers 16:42–50

US National Library of Medicine, National Institutes of Health (2011) PubMed home page. http://preview.ncbi.nlm.nih.gov/pubmed

Vesely K, Jurajda M, Nenutil R, Vesela M (2009) Expression of p53, cyclin D1 and EGFR correlates with histological grade of adult soft tissue sarcomas: a study on tissue microarrays. Neoplasma 56:239–244

Vogelstein B, Lane D, Levine AJ (2000) Surfing the p53 network. Nature 408:307–310

Wunder JS, Eppert K, Burrow SR, Gokgoz N, Bell RS, Andrulis IL (1999) Co-amplification and overexpression of CDK4, SAS and MDM2 occurs frequently in human parosteal osteosarcomas. Oncogene 18:783–788

Yang M, Guo Y, Zhang X, Miao X, Tan W, Sun T, Zhao D, Yu D, Liu J, Lin D (2007) Interaction of P53 Arg72Pro and MDM2 T309G polymorphisms and their associations with risk of gastric cardia cancer. Carcinogenesis 28:1996–2001

Yu W, Gwinn M, Clyne M, Yesupriya A, Khoury MJ (2008) A navigator for human genome epidemiology. Nat Genet 40:124–125