Short Research Communication

Association of the *TP53* rs1042522 C>G polymorphism and hepatoblastoma risk in Chinese children

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Abstract

The *TP53* gene encodes an important class of cell cycle and tumor-suppressing factors that play critical roles in maintaining genomic stability. The *TP53* Arg72Pro (rs1042522 C>G) polymorphism has been reported to be associated with the risk of several types of adult cancers; however, its risk for pediatric cancers remains unclear. Here, we analyzed the association of the *TP53* gene rs1042522 C>G polymorphism with hepatoblastoma (HB) susceptibility in a hospital-based study among Chinese children. A total of 213 HB patients and 958 healthy controls were enrolled in the study. Genotypes were determined by a TaqMan assay, and the strength of the association was assessed by the odds ratios and 95% confidence intervals generated from logistic regression models, adjusted for age, gender, and clinical stage. No significant association between the *TP53* rs1042522 C>G polymorphism and HB susceptibility was detected in the main analysis or in stratification analyses of age, gender, and clinical stages. Overall, the *TP53* gene rs1042522 C>G polymorphism is not associated with HB susceptibility in the Chinese population, other polymorphisms alone or in combination should be investigated to further clarify HB susceptibility.

Key words: *TP53*; rs1042522 C>G; polymorphism; genetic association; hepatoblastoma

Introduction

Hepatoblastoma (HB) is an embryonic tumor derived from hepatic precursor cells, and is the most common hepatic malignancy in children, accounting for approximately 80% of all childhood liver tumors [1, 2]. HB predominantly occurs in children under the age of 5 years, although those aged between 6 months and 3 years have the highest incidence, and the median age is 17 months, with a greater incidence in boys [3]. An enlarged hepatic mass and increased alpha fetoprotein level are the main clinical features of HB [4]. Complete surgical resection remains the mainstay treatment, and neoadjuvant and postoperative chemotherapy help to substantially increase overall survival [5].

Although most HB cases are sporadic, some patients also have a family history of cancers and certain cases are associated with genetic aberrations. HB is also associated with Edwards syndrome, Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and other genetic syndromes [6], which can significantly increase the risk of developing HB [7, 8]. HB development has been linked to abnormal methylation of certain imprinted differentially methylated regions in tumor-specific genes, such as 11p15.5 and 20q13.3, which have high rates of genetic and epigenetic changes along with

abnormally high expression [9]. In addition, HB development has been associated with abnormal Wnt signaling pathway activation due to somatic or germline mutations of various genes [10]. Besides these specific factors, HB has been linked to chromosomal abnormalities, genetic factors, low birth weight, and various adverse factors during pregnancy, either acting alone or in combination [11].

The treatment and prognosis of HB is currently based on a risk stratification system. Complete surgical resection is generally curative for well-differentiated fetal HB, while chemotherapy is needed for other subtypes, and a cisplatin-based chemotherapy regimen is particularly effective [12]. With state-of-the-art treatment, the 5-year overall survival rate of HB is over 70% [11]. However, treatment of cases associated with high risk factors remains challenging. Therefore, further investigation is warranted to unveil the detailed pathogenesis and enable better prognosis.

TP53 is an important tumor suppressor gene, located on chromosome 17p13.1 comprising 11 exons and 10 introns. *TP53* encodes a protein of 393 amino acids, which has three major domains: an N-terminal transactivation site, intermediate DNA-binding region, and C-terminal oligomerization site [13]. *TP53* exerts important biological functions by regulating the cell cycle, promoting cell apoptosis, participating in DNA recombination and repair, and stabilizing genome function. Moreover, TP53 protein can stimulate the expression of genes involved in the inhibition of angiogenesis, which may further prevent tumor formation [14, 15].

Given these important functions, a variety of malignancies may occur when the *TP53* gene is inactivated [15]. Among those genetic variants that impact gene function, single nucleotide polymorphism (SNP) plays an important role [16, 17]. Potentially functional SNPs located within cell death genes may influence cancer risk in various ways [18-21]. To date, more than 200 polymorphic loci have been detected in *TP53* [22], and the three major single nucleotide polymorphisms are associated with tumorigenesis [23]. The first is a single nucleotide polymorphism (rs1042522 C>G; CGC-CCC) located at codon 72 of exon 4 of *TP53*, which results in substitution of an arginine (Arg) to proline (Pro) residue in the protein [24]. The second polymorphism is a 16-bp insertion repeat in the third intron region of *TP53* [25, 26]. The third polymorphism occurs at the MSP I restriction site of *TP53* in the sixth intron [27]. Among these three polymorphisms, rs1042522 C>G is the most important and extensively investigated one [28]. Several studies have shown that these three polymorphisms are associated with the genetic susceptibility of many tumors [26, 29, 30]. In particular, the *TP53* rs1042522 C>G polymorphism is associated with susceptibility to multiple malignancies such as breast cancer, lung cancer, and cervical cancer [28, 31-33], suggesting that this part of the gene plays an important role in the development of adult cancers. However, the influence of the *TP53* rs1042522 C>G polymorphism has not been investigated in HB.

Therefore, in this study, we analyzed the relationship between the *TP53* gene rs1042522 C>G polymorphism and HB susceptibility in a cohort of children with HB and healthy controls in the Han Chinese population.

Materials and Methods

Study subjects

A total of 213 HB patients and 958 healthy control subjects from Chinese genetically unrelated Han people were enrolled in the study, including subjects from four hospitals in Guangdong province, Henan province, Shaanxi province, and Shannxi province (**Supplemental Table 1**). All patients were younger than 18 years and were diagnosed as having HB based on a histopathological examination. None of the patients had a history of any other tumors. The control subjects were randomly chosen among children living in the same area as the HB patients, with match age and sex.

This study was approved by the Institutional Review Board of Guangzhou Women and Children's Medical Center (Guangzhou, China). Informed consent for participation in the study was obtained from the legal guardians of all subjects. All patient records were anonymized and de-identified prior to analysis.

Genotyping

The *TP53* gene rs1042522 C>G polymorphism was genotyped on a TaqMan platform (Applied Biosystems, Foster City, CA, USA) as reported previously [34-36]. Quality control was performed with eight negative control and positive control samples in each 384-well plate. In addition, 10% of the samples were randomly selected for a second genotyping for validation of the assay, and the concordance rate was 100%.

Statistical analysis

The χ^2 test was used to detect differences in demographic variables, risk factors distribution, and *TP53* genotype distribution between the case and control groups. The χ^2 was also used to test whether the distribution of *TP53* genotypes was consistent with Hardy-Weinberg equilibrium (HWE)

expectations. Univariate and multivariate unconditional logistic regression analyses were used to test the association of single nucleotide polymorphism genotypes with HB risk based on the generated odds ratios (ORs) and 95% confidence intervals (CIs). Adjusted ORs were calculated using multivariate analysis adjusting for age, and gender. The χ^2 test and logistic regression analysis were used to analyze the statistical differences in age, gender, and clinical stage of HB patients with different genotypes. Polymorphic loci were evaluated by dominant and recessive models, according to the *P* values, ORs, and 95% CIs. All statistical analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC). *P* < 0.05 was considered to indicate a statistically significant difference or association.

Results

Characteristics of the study population

Overall, the frequency distribution of selected variables did not differ between HB patients and controls. The distributions of age, gender, and clinical stages of the study subjects are summarized in **Table 1**. There was no significant difference between HB patients and controls regarding the distribution of age (*P* = 0.105) and gender (*P* = 0.973). Males were predominant in both the HB and control groups. Most of the patients had stage II disease, followed by stage I, stage III, and stage IV. There were also no significant differences in the age and gender distribution between HB patients and healthy control recruited from each province (*P* > 0.05).

TP53 rs1042522 C>G polymorphism and HB susceptibility

The genotype distributions of the *TP53* rs1042522 C>G polymorphism in HB patients and controls are summarized in **Table 2**. Three genotypes, CC, CG, and GG, were detected at the rs1042522 locus of *TP53* gene, with similar frequencies of each genotype in the two groups, although the frequencies of the CC and GG genotypes were slightly higher in HB cases, whereas the CG frequency was slightly higher in controls. No significant deviation from HWE was detected in the control group (*P* = 0.485). Moreover, there was no significant association observed between the *TP53* rs1042522 C>G polymorphism and HB susceptibility in any comparison (**Table 2**).

Stratification analysis of the *TP53* rs1042522 C>G polymorphism and HB risk

We further explored the association between the *TP53* rs1042522 C>G polymorphism and HB risk in analyses stratified by age, gender, and clinical stages (**Table 3**). No significant associations were observed in children older than 17 months or in those 17 months or younger. In addition, the CG/GG genotypes were not significantly associated with HB risk in either females or males. Finally, CG/GG genotypes were not associated with HB risk in patients at stage I+II or stage III+IV.

Table 1. Frequency distribution of selected variables in hepatoblastoma patients and controls

Variables	Cases (n = 213)		Controls (n = 958)		P^a
	No.	%	No.	%	
Age range, months	0.23–149.97		0.004–156.00		0.105
Mean ± SD	23.62 ± 24.36		23.75 ± 18.30		
<17	114	53.52	454	47.39	
≥17	99	46.48	504	52.61	
Gender					0.973
Female	84	39.44	379	39.56	
Male	129	60.56	579	60.44	
Clinical stage					
I	42	19.72			
II	55	25.82			
III	40	18.78			
IV	15	7.04			
NA	61	28.64			

ᵃ Based on a two-sided χ^2 test for distributions between hepatoblastoma patients and cancer-free controls.

Discussion

Overall, this first hospital-based case-control study of its kind indicates that the *TP53* gene rs1042522 C>G polymorphism may not be associated with HB susceptibility in Chinese children.

HB is a malignant embryonic tumor and is the most common hepatic malignancy in children [37]. Although the overall incidence is relatively low, with an annual incidence rate of confirmed cases of 1 in 1,000,000 children up to 18 months old [38], recent studies indicate an increasing trend. In particular, the number of HB cases doubled from 1975 to 2009, and has increased by about 4% per year from 1992 to 2004, representing an emerging threat to children's health [39].

Inactivation of the *TP53* tumor suppressor gene is associated with an increased risk of a variety of malignant tumors [40]. Specifically, *TP53* gene polymorphisms have been associated with the susceptibility to many cancers [32]. Moreover, rare variants in *TP53* gene also contribute to childhood neuroblastoma susceptibility [41]. The rs1042522 C>G polymorphism of *TP53* is the most extensively studied and of paramount importance for cancer risk [33]. Although the polymorphism results in the same basic structure of the TP53 protein as the wild-type, the molecular biological behavior and functions are different [42].

Table 2. Association between *TP53* rs1042522 C>G polymorphism and hepatoblastoma susceptibility

Genotype	Cases n (%)	Controls n (%)	P [a]	Crude OR (95% CI)	P	Adjusted OR (95% CI) [b]	P [b]
rs1042522 C>G (HWE = 0.485)							
CC	70 (32.86)	284 (29.65)		1.00		1.00	
CG	99 (46.48)	485 (50.63)		0.83 (0.59–1.16)	0.276	0.83 (0.59–1.16)	0.274
GG	44 (20.66)	189 (19.73)		0.95 (0.62–1.44)	0.790	0.94 (0.62–1.44)	0.790
Additive			0.529	0.95 (0.77–1.18)	0.666	0.95 (0.77–1.18)	0.666
Dominant	143 (67.14)	674 (70.35)	0.355	0.86 (0.63–1.18)	0.355	0.86 (0.63–1.18)	0.354
Recessive	169 (79.34)	769 (80.27)	0.759	1.06 (0.73–1.53)	0.759	1.06 (0.73–1.53)	0.758

[a] Based on a χ^2 test for genotype distributions between hepatoblastoma cases and cancer-free controls.
[b] Adjusted for age and gender.

Table 3. Stratification analyses for the association between *TP53* rs1042522 C>G polymorphism and hepatoblastoma susceptibility

Variables	CC	CG/GG	Crude OR	P	Adjusted OR [a]	P [a]
	(Cases/Controls)		(95% CI)		(95% CI)	
Age, months						
<17	36/129	78/325	0.86 (0.55–1.34)	0.506	0.86 (0.55–1.34)	0.499
≥17	34/155	65/349	0.85 (0.54–1.34)	0.482	0.85 (0.54–1.34)	0.483
Gender						
Females	27/118	57/261	0.95 (0.58–1.59)	0.857	0.95 (0.57–1.57)	0.833
Males	43/166	86/413	0.80 (0.54–1.21)	0.294	0.81 (0.54–1.21)	0.298
Clinical stages						
I+II	28/284	69/674	1.04 (0.66–1.65)	0.874	1.04 (0.66–1.65)	0.858
III+IV	23/284	32/674	0.59 (0.34–1.02)	0.059	0.59 (0.34–1.03)	0.062

[a] Adjusted for age and gender, omitting the corresponding stratification factor.

The polymorphic TP53 Pro-type protein shows stronger transcriptional activity than the wild-type TP53 Arg protein and up-regulates downstream gene expression [43]. By contrast, the Arg-type TP53 protein not only has a stronger inhibition function on transformed cell growth than TP53 Pro but also exhibits a stronger function of promoting cell apoptosis and repairing cell damage [44]. In addition, the TP53 Arg-type protein is easily degraded by the high-risk HPV E6 protein, whereas the TP53 Pro-type protein is not degraded by E6 [45].

With this increased understanding of the different biological functions of TP53 Pro and TP53 Arg proteins, many studies have demonstrated that the rs1042522 C>G polymorphism was associated with increased susceptibility to various cancers, including breast cancer, lung cancer, thyroid cancer, and cervical cancer [29, 46-48]. The first *TP53* Arg/Pro polymorphism with cancer susceptibility were discovered in 1998, in which Rosenthal et al. [49] found that British women that were homozygous for *TP53* Arg tended to have a 7-fold increased risk of cervical cancer compared with those harboring the heterozygous *TP53* Pro/Arg and homozygous *TP53* Pro forms.

In the present study, we genotyped 213 HB patients and 958 cancer-free controls from four different hospitals across China to evaluate the association between the *TP53* gene rs1042522 C>G polymorphism and HB susceptibility. Although our overall results suggest no association, it is important to consider that HB is a multi-factorial disease resulting from multiplicative interactions between environmental factors and genetic backgrounds. Thus, a main limitation of this study is the lack of available information on some valuable parameters such as parental exposure, dietary intake, and living environment. Selection bias is another obvious potentially confounding factor, as the study population certainly is not representative of the whole Chinese population.

Moreover, the analysis of this study is limited by at least the three following points. First, the number of HB patients included in the study is relatively small, which could have weakened the statistical power. Second, we only focused on one polymorphism, and thus the potential associations of other known polymorphisms of the *TP53* gene with HB risk, alone or in combination, should be investigated. Third, as mentioned above, the interaction of environmental factors with the polymorphism was not addressed. Thus, to better elucidate the role of the *TP53* polymorphism with HB susceptibility, future study designs should try to avoid these shortcomings as much as possible.

Despite these limitations, this study represents the largest case-control study conducted to date to explore the correlation between the *TP53* rs1042522 C>G polymorphism and HB risk in the Chinese population. We found no such risk, pointing to a need for further validation of this association in other populations, as well as in other forms of pediatric cancers. Moreover, further investigations of polymorphisms that might mediate the risk of HB would help gain a better understanding of the pathogenesis and improve prognosis in the face of the increasing incidence of this otherwise rare malignancy in children.

Abbreviations

HB, hepatoblastoma; SNP, single nucleotide polymorphism; Arg, arginine; Pro, proline; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

Supplementary Material

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

References

1. von Schweinitz D. Hepatoblastoma: recent developments in research and treatment. Semin Pediatr Surg. 2012; 21: 21-30.
2. Herzog CE, Andrassy RJ, Eftekhari F. Childhood cancers: hepatoblastoma. Oncologist. 2000; 5: 445-53.
3. McCarville MB, Roebuck DJ. Diagnosis and staging of hepatoblastoma: imaging aspects. Pediatr Blood Cancer. 2012; 59: 793-9.
4. Koh KN, Park M, Kim BE, Bae KW, Kim KM, Im HJ, et al. Prognostic implications of serum alpha-fetoprotein response during treatment of hepatoblastoma. Pediatr Blood Cancer. 2011; 57: 554-60.
5. Ang JP, Heath JA, Donath S, Khurana S, Auldist A. Treatment outcomes for hepatoblastoma: an institution's experience over two decades. Pediatr Surg Int. 2007; 23: 103-9.
6. Stocker JT, Ishak KG. Hepatoblastoma. Semin Diagn Pathol. 1994; 11: 136-43.
7. Goldman LJ, Nodal C, Jimenez E. Successful airway control with the laryngeal mask in an infant with Beckwith-Wiedemann syndrome and hepatoblastoma for central line catheterization. Paediatr Anaesth. 2010; 10: 445-8.
8. Hughes LJ, Michels VV. Risk of hepatoblastoma in familial adenomatous polyposis. Am J Med Genet. 2010; 43: 1023-5.
9. Rumbajan JM, Maeda T, Souzaki R, Mitsui K, Higashimoto K, Nakabayashi K, et al. Comprehensive analyses of imprinted differentially methylated regions reveal epigenetic and genetic characteristics in hepatoblastoma. BMC Cancer. 2013; 13: 608.
10. Ueda Y, Hiyama E, Kamimatsuse A, Kamei N, Ogura K, Sueda T. Wnt signaling and telomerase activation of hepatoblastoma: correlation with chemosensitivity and surgical resectability. J Pediatr Surg. 2011; 46: 2221-7.
11. Trobaugh-Lotrario AD, Katzenstein HM. Chemotherapeutic approaches for newly diagnosed hepatoblastoma: past, present, and future strategies. Pediatr Blood Cancer. 2012; 59: 809-12.
12. Tiao GM, Bobey N, Allen S, Nieves N, Alonso M, Bucuvalas J, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. J Pediatr. 2005; 146: 204-11.
13. Mcbride OW, Merry D, Givol D. The gene for human p53 cellular tumor antigen is located on chromosome 17 short arm (17p13). Proc Natl Acad Sci U S A. 1986; 83: 130-4.
14. Levine AJ. p53, the cellular gatekeeper for growth and division. Cell. 1997; 88: 323-31.
15. Whibley C, Pharoah PD, Hollstein M. p53 polymorphisms: cancer implications. Nat Rev Cancer. 2009; 9: 95-107.
16. Chang J, Tian J, Yang Y, Zhong R, Li J, Zhai K, et al. A Rare Missense Variant in TCF7L2 Associates with Colorectal Cancer Risk by Interacting with a GWAS-Identified Regulatory Variant in the MYC Enhancer. Cancer Res. 2018; 78: 5164-72.
17. Chang J, Tian J, Zhu Y, Zhong R, Zhai K, Li J, et al. Exome-wide analysis identifies three low-frequency missense variants associated with pancreatic cancer risk in Chinese populations. Nat Commun. 2018; 9: 3688.
18. Chang J, Zhong R, Tian J, Li J, Zhai K, Ke J, et al. Exome-wide analyses identify low-frequency variant in CYP26B1 and additional coding variants associated with esophageal squamous cell carcinoma. Nat Genet. 2018; 50: 338-43.
19. Li J, Chang J, Tian J, Ke J, Zhu Y, Yang Y, et al. A Rare Variant P507L in TPP1 Interrupts TPP1-TIN2 Interaction, Influences Telomere Length, and Confers Colorectal Cancer Risk in Chinese Population. Cancer Epidemiol Biomarkers Prev. 2018; 27: 1029-35.
20. Capasso M, McDaniel LD, Cimmino F, Cirino A, Formicola D, Russell MR, et al. The functional variant rs34330 of CDKN1B is associated with risk of neuroblastoma. J Cell Mol Med. 2017; 21: 3224-30.
21. Capasso M, Diskin S, Cimmino F, Acierno G, Totaro F, Petrosino G, et al. Common genetic variants in NEFL influence gene expression and neuroblastoma risk. Cancer Res. 2014; 74: 6913-24.
22. Pietsch EC, Humbey O, Murphy ME. Polymorphisms in the p53 pathway. Oncogene. 2006; 25: 1602-11.
23. Naccarati A, Polakova V, Pardini B, Vodickova L, Hemminki K, Kumar R, et al. Mutations and polymorphisms in TP53 gene--an overview on the role in colorectal cancer. Mutagenesis. 2012; 27: 211-8.
24. Pim D, Banks L. p53 polymorphic variants at codon 72 exert different effects on cell cycle progression. Int J Cancer. 2004; 108: 196-9.
25. Costa S, Pinto D, Pereira D, Rodrigues H, Cameselle-Teijeiro J, Medeiros R, et al. Importance of TP53 codon 72 and intron 3 duplication 16bp polymorphisms in prediction of susceptibility on breast cancer. BMC Cancer. 2008; 8: 32.
26. Eskandari-Nasab E, Hashemi M, Amininia S, Ebrahimi M, Rezaei M, Hashemi SM. Effect of TP53 16-bp and beta-TrCP 9-bp INS/DEL polymorphisms in relation to risk of breast cancer. Gene. 2015; 568: 181-5.
27. Tan C, Xu HY, Zhang CY, Zhang H, Chen CM, Zhang WM, et al. Effect of CYP1A1 MSPI polymorphism on the relationship between TP53 mutation and CDKN2A hypermethylation in non-small cell lung cancer. Arch Med Res. 2011; 42: 669-76.
28. He J, Wang FH, Zhu JH, Zhang ZR, Zou Y, Zhang RZ, et al. The TP53 gene rs1042522 C > G polymorphism and neuroblastoma risk in Chinese children. Aging (Albany NY). 2017; 9: 852-9.
29. Fernández-Rubio A, López-Cima MF, González-Arriaga P, García-Castro L, Pascual T, Marrón MG, et al. The TP53 Arg72Pro polymorphism and lung risk in a population of Northern Spain. Lung Cancer. 2008; 61: 309-16.
30. Laprano TD, Lemos EH, Cunha LM, Junior JE, de SousaTeles RA, Rabenhorst SH. Association of TP53 codon 72 and intron 3 16-bp Ins/Del polymorphisms with cervical cancer risk. Tumour Biol. 2014; 35: 7435-40.
31. Sonoyama T, Sakai A, Mita Y, Yasuda Y, Kawamoto H, Yagi T, et al. TP53 codon 72 polymorphism is associated with pancreatic cancer risk in males, smokers and drinkers. Mol Med Rep. 2011; 4: 489-95.
32. Dong ZY, Zheng LZ, Liu WM, Wang CC. Association of mRNA expression of TP53 and the TP53 codon 72 Arg/Pro gene polymorphism with colorectal cancer risk in Asian population: a bioinformatics analysis and meta-analysis. Cancer Manag Res. 2018; 10: 1341-9.
33. Fu W, Zhuo ZJ, Jia W, Zhu JH, Zhu SB, Lin ZF, et al. Association between TP53 gene Arg72Pro polymorphism and Wilms' tumor risk in a Chinese population. Onco Targets Ther. 2017; 10: 1149-54.
34. He J, Wang F, Zhu J, Zhang R, Yang T, Zou Y, et al. Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. J Cell Mol Med. 2016; 20: 1481-90.
35. He J, Zou Y, Wang T, Zhang R, Yang T, Zhu J, et al. Genetic Variations of GWAS-Identified Genes and Neuroblastoma Susceptibility: a Replication Study in Southern Chinese Children. Transl Oncol. 2017; 10: 936-41.
36. He J, Zou Y, Liu X, Zhu J, Zhang J, Zhang R, et al. Association of Common Genetic Variants in Pre-microRNAs and Neuroblastoma Susceptibility: A Two-Center Study in Chinese Children. Mol Ther Nucleic Acids. 2018; 11: 1-8.
37. Rai P, J HF. Cerebral Metastasis of Hepatoblastoma: A Review. J Pediatr Hematol Oncol. 2016; 38: 279-82.
38. El Asmar A, El Rassi Z. Hepatoblastoma in childhood, long term survival achieved: 2 case reports and literature review. Int J Surg Case Rep. 2016; 21: 55-8.
39. Devi LP, Kumar R, Handique A, Kumar M. Hepatoblastoma--a rare liver tumor with review of literature. J Gastrointest Cancer. 2014; 45 Suppl 1: 261-4.
40. Borges LM, Ayres FM. R337H mutation of the TP53 gene as a clinical marker in cancer patients: a systematic review of literature. Genet Mol Res. 2015; 14: 17034-43.
41. Diskin SJ, Capasso M, Diamond M, Oldridge DA, Conkrite K, Bosse KR, et al. Rare variants in TP53 and susceptibility to neuroblastoma. J Natl Cancer Inst. 2014; 106: dju047.

42. Ignacio RMC, Lee ES, Wilson AJ, Beeghly-Fadiel A, Whalen MM, Son DS. Chemokine Network and Overall Survival in TP53 Wild-Type and Mutant Ovarian Cancer. Immune Netw. 2018; 18: e29.

43. Pandith AA, Khan NP, Rashid N, Azad N, Zaroo I, Hafiz A, et al. Impact of codon 72 Arg > Pro single nucleotide polymorphism in TP53 gene in the risk of kangri cancer: a case control study in Kashmir. Tumour Biol. 2012; 33: 927-33.

44. Dahabreh IJ, Schmid CH, Lau J, Varvarigou V, Murray S, Trikalinos TA. Genotype Misclassification in Genetic Association Studies of the rs1042522 TP53 (Arg72Pro) Polymorphism: A Systematic Review of Studies of Breast, Lung, Colorectal, Ovarian, and Endometrial Cancer. Am J Epidemiol. 2013; 177: 1317-25.

45. Yan L, Zhang D, Chen C, Mao Y, Xie Y, Li Y, et al. TP53 Arg72Pro polymorphism and lung cancer risk: A meta-analysis. Int J Cancer. 2010; 125: 2903-11.

46. Hossain A, Murshid GMM, Zilani MNH, Islam F, Sultana R, Sultana T, et al. TP53 codon 72 polymorphism and breast cancer risk in Bangladeshi population. Breast Cancer. 2017; 24: 571-8.

47. Khan MS, Pandith AA, Masoodi SR, Khan SH, Rather TA, Andrabi KI, et al. Significant association of TP53 Arg72Pro polymorphism in susceptibility to differentiated thyroid cancer. Cancer Biomark. 2015; 15.

48. Klug SJ, Ressing M, Koenig J, Abba MC, Agorastos T, Brenna SMF, et al. TP53 codon 72 polymorphism and cervical cancer: a pooled analysis of individual data from 49 studies. Lancet Oncol. 2009; 10: 772-84.

49. Rosenthal AN, Ryan A, Aljehani RM, Storey A, Harwood CA, Jacobs IJ. p53 codon 72 polymorphism and risk of cervical cancer in UK. Lancet. 1998; 352: 0-872.