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P53 Codon 72 Gene Polymorphism and Risk of Oral Squamous Cell Carcinoma in South Indian Population: A Case-Control Study

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Abstract

Background: The *p53* protein has pleiotropic functions in the modulation of genomic stability of cells. Disruption of *p53* activity is commonly found in human cancers. The *p53* codon 72 polymorphism is likely to play an important role in the susceptibility to OSCC. We aimed to investigate the association of *p53* codon 72 polymorphism with oral squamous cell carcinoma in south Indian population.

Methods: We genotyped 150 OSCC patients and 150 controls, using PCR-RFLP method.

Results: Our results showed a significant difference in the distributions of *p53* codon 72 genotypes among cases and controls. Genotype frequencies of *p53* Arg/Arg, Arg/Pro and Pro/Pro were 50.8, 33.9 and 14.4% in the oral squamous cell carcinoma patients and 48.7, 45.1 and 6.2% in the controls, respectively. Arginine/arginine genotype was elevated in controls compared to patients (P<0.0001), where as Proline/Proline (P<0.005) and arginine/proline (P<0.002) genotypes were elevated in patients compared to controls. Arginine allele frequency showed high in cases than Proline.

Conclusion: The results of the present study detected that *p53* codon 72 polymorphism may contribute to oral squamous cell carcinoma susceptibility in south Indian population.

Keywords: Oral squamous cell carcinoma; Arg72Pro; PCR-RFLP; Polymorphism; TP53

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignant neoplasms worldwide. Oral cancer forms a large part of the cancer load in the part of India [1]. Smoking, alcohol, drinking, viral infection and genetic factors are the major risk factors involved in the etiology of oral squamous cell carcinoma. Some molecular studies have provided some clues to the molecular mechanisms underlying such genetic susceptibility, and it is likely that they are genetically determined. DNA repair capacity may contribute to interindividual variation in susceptibility to head and neck carcinogenesis. The tumour suppressor gene *p53* is crucial for host defence against genomic mutations which might cause many types of tumours. The *p53* protein has pleiotropic functions in the modulation of genomic stability of cells. Disruption of *p53* activity is commonly found in human cancers. The production of *p53* is increased in response to cellular insults or DNA damage, and *p53* then induces cell cycle arrest at the G_1/S junction. If the damage is irreparable, *p53* can initiate cell death by apoptosis [2]. Mutant proteins are defective in DNA binding in a sequence-specific manner, and thus in the upregulation of downstream genes [3]. So far 13 polymorphisms have been described in this gene [4]. The most commonly studied one is a single nucleotide polymorphism (SNP) at codon 72 in exon four of the *p53* gene, which results in the substitution of arginine (Arg) by proline (Pro) in the transactivating domain. These two polymorphic variants (Pro72 and Arg72) alter the structure and function of the *p53* protein [5]. The potential consequence of this amino acid exchange is differences in the susceptibility to malignant transformation, induction of apoptosis, and transcriptional activity [6]. The arginine (Arg72) allele increases the ability of *p53* to locate to mitochondria and induce cellular death, whereas proline allele (Pro72) exhibits a lower apoptotic potential and an increased cellular arrest in G1 of the cell cycle [7].

Several epidemiological surveys reported association and non association of this codon 72 (Arg/Pro) polymorphism with different types of cancers [8], it suggests that Pro72 Pro genotype may be the potential risk factor favoring the development of lung carcinoma in Kerala population and Arg72Pro genotype is independently associated with a poorer prognosis of lung cancer**.** De Chaudhuri, et al. [9], in a study reported that individuals carrying the arginine homozygous genotype at codon 72 and no duplication homozygous genotype at intron three are at risk for the development of arsenic induced keratosis. Rajkumar et al. [10], study reported that SNP's can help predict breast cancer risk in south Indian women. Sailaja et al. [11], suggests that proline genotype might confer increased risk to develop CML in Hyderabad population and is also associated with poor cytogenetic response. In Mumbai population equidistribution of the genotypes were detected in both normal controls and oral cancer patients. Thus Tandle et al. [12], in a study reported that Association of *p53* genotypes with oral cancer was not detected. In contrast, to above investigations investigators in some studies demonstrated the non association between the different *p53* polymorphisms and individual cancer development, other studies revealed the higher risks in the individuals with *p53**Pro72 homozygote. The aim of the present study is to identify whether TP53 codon 72 polymorphism can be considered

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as risk factor for developing oral squamous cell carcinoma in south Indian population and its impact on disease progression.

Materials and Methods

Study population

Oral squamous cell carcinoma patients were assessed on the basis of clinical and pathological examinations. This study is a Hospital-based case-control study conducted on South Indian population. All incidents of OSCC cases are newly diagnosed during the study period, Ethical committee approved the study. The procedures followed according to the ethical standards of responsible committee of the Institutes/Hospitals, to participate in a face-to-face interview using a structured questionnaire.

Selection criteria

Senior pathologists confirmed all diagnoses. We interviewed and collected the demographic factors data from the patient. We collected the information on age, smoking, chewing, usual alcohol intake, and previous cancer diagnoses. Participant's family history of cancer and the clinical information for these cases are obtained from medical records, tumor size, stage, and chemotherapy drugs. Patients were recruited based on inclusion and exclusion criteria, which were determined before the beginning of the study.

Inclusion and exclusion criteria

All new cases of clinically confirmed oral squamous cell carcinoma would be taken for study. Patients of confirmed oral carcinoma who give their consent were included. Patients who refuse to give consent and cases of oral cancer other than squamous cell carcinoma are excluded.

Sample collection

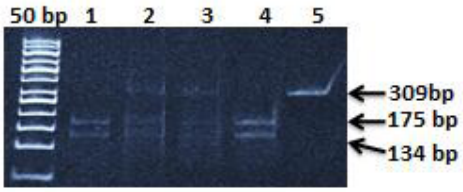
A total of 150 OSCC patients and 150 age-matched controls are enrolled in the study. Sampling was done from one major hospital, MNJ cancer Institute in Hyderabad, Andhra Pradesh between the periods June 2008 to March 2010.

Collection of blood samples

3 ml of blood samples were collected from pathology lab after diagnosis. All the samples diagnosed mainly as oral squamous cell carcinoma. Blood sample were collected from healthy individuals (voluntarily) by venipuncture. These samples are used as controls.

Genotyping of the *P53* codon 72 polymorphism

Genomic DNA was extracted from whole blood according to standard procedures used by our group [13]. PCR amplification was carried out using following primers, 5' TTCACCCATCTACAGTCC 3' and 5' CTCAGGGCAACTGACCGT 3' synthesized at Bioserve Biotechnologies (Hyderabad, India). Three steps PCR amplification was performed as described earlier, briefly a 25 µl reaction was set up containing 0.2 mM of each dNTP, 1X buffer, 1.5 mM $MgCl_2$ and 2U of Taq DNA polymerase (Bioserve, India). 30 cycles were performed with denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds and elongation at 72°C for 30 seconds. The PCR amplification was checked on a 3% agarose gel. 10 µl PCR reaction mix was subsequently digested with *BstUI (Bsh1236I)* restriction enzyme (Fermatas, USA). PCR product of 309-bp indicating Proline/Proline after digestion gave two bands of 175bp and 134bp showing Arginine/Arginine and three bands of 309, 175 and 134 bp indicating Arginine/Proline (Figure 1 and 2). Statistical analysis was performed using Medical (Version 10.3.1) statistical software (Belgium).



Lane: 50bp Marker
Lane: 1 & 4: 175bp &134bp (Arginine/Arginine)
Lane: 2 & 3: 309bp, 175bp & 134bp (Arginine/Proline)
Lane: 5: 309bp (Proline/Proline)

Figure 1: P53 Codon 72 polymorphism RFLP Gel picture.

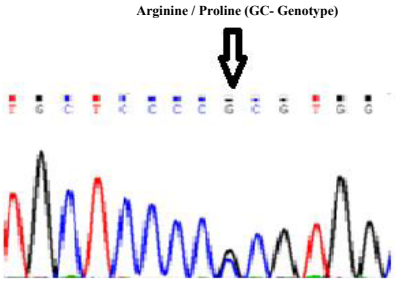


Figure 2: P53 Codon 72 polymorphism sequence picture.

Results

Biological characteristics

The distribution patient's biological characteristics and selected risk factors are shown in Table 1. Age range for OSCC patients was 9-87 years in males and 27-75 in years in females and in controls 21-80 years in males and 22-87 years in females. However, many of the ages mentioned in case sheets or given by patients were arbitrary, exact age of 150 OSCC patients (Males 81 and Females 69) and 150 controls (Males 91 and Females 59) was available, hence analysis was carried out with those, mean age at which OSCC identified as 9-87/ 49.30 ± 15.55 in males and 27-75/84.20 ± 11.26 in females years. To understand the role of gene mutations/ polymorphisms in onset of the disease, the patients were divided into 4 categories, <25 years (1.33%), 26 to 45 years (32.00%), 46 to 65 years (54.00%), and above 66 years (20.12%). Highest percentage of OSCC patients was identified between 46-65 years. Regarding the primary tumor site, there was a neat predominance on the BM adding up 56 patients (37.33%), followed by tongue adding up 33 patients (22.0%), then mandible, oral cavity and RMT adding up 12%, 10% and 7%. In the present study, high percentage was identified in BM patients and low percentage was observed in BOT, FOM maxilla, palate and lip sites. The stage of a cancer is a descriptor (usually numbers I to IV) of how much the cancer has spread. The stage often takes into account the size of a tumor, In the present study Stage III showed the highest frequency (40%) when compared to Stage II (22%) and Stage IV (31.33%), and other types of tumor grade like Stage I (6.67%) showed very low frequency when compared to other staging groups. The percentage of patients with family history was 5% in oral squamous cell carcinoma patients In the present study majority of patients 40.7% had received radiation therapy

Demographical Characteristics	No. (%) N = 150
Gender	
Males	81 (54.0)
Females	69 (46.0)
Range/Mean (males)	9-87/ 49.30 ± 15.55
Range/Mean (females)	27-75/84.20 ± 11.26
Age Distribution	
<25	2 (1.33)
26-45	48 (32.00)
46-65	81 (54.00)
66 and above	19 (12.67)
Site of Diagnosis	
BM	56 (37.33)
Tongue	33 (22.00)
BOT	2 (1.3)
FOM	6 (4.00)
LIP	4 (2.67)
Mandible	18 (12.00)
Maxilla	3 (2.00)
Palate	3 (2.00)
RMT	11 (7.33)
Oral Cavity	14 (9.3)
Staging	
Stage 1	10 (6.67)
Stage 2	33 (22.00)
Stage 3	60 (40.00)
Stage 4	47 (31.33)
Habitual Risk	
Alcoholic status	
Alcoholics	2 (1.3)
Smoking Status	
Smokers	12 (8.0)
Chewing Status	
Chewing	46 (30.6)
Combination Risk Factors	
Alcohol + Smoking	19 (12.6)
Alcohol + Chewing	35 (23.33)
Smoking + Chewing	4 (2.6)
Alcohol + Smoking + Chewing	15 (10.0)
No Habits	17 (11.33)

Table 1: Demographic details of individuals included in the study.

with adjuvant chemotherapy, 23.3% underwent surgery, followed by surgery with adjuvant chemotherapy 14.0%. 13.3% and 0.7% of the patients received radiation and chemotherapy alone. Surgical excision and/or adequate radiation therapy remain the most effective means of treating the patients with OSCC.

Distribution of *p53* genotypes/alleles in OSCC patients and controls

In the present study, OSCC patients showed 58.66% GG, 26.66% GC and 14.66% CC genotypes when compared to controls that had 82.66% GG, 12.66% GC and 4, 6% CC genotypes. It was observed that codon 72 polymorphism was significantly associated with OSCC. The frequency of arginine/arginine genotype was elevated in OSCC in controls compared to patients (P<0.0001), where as frequency of arginine/arginine (OR. 3.51, 95% CI 1.45-8.49, P<0.005) and arginine/proline (OR. 2.50, 95% CI 1.37-4.57, P<0.002) genotypes were elevated in patients compared to controls (Table 2).

P53 genotypes and clinocopathological characteristics of oral squamous cell carcinoma

We further stratified the associations between the *p53* genotypes and age, site, stage smoking and alcohol drinking to understand the influence of *p53* codon 72 polymorphism on the OSCC risk. The frequency of Arginine allele was found to be high in median age group (46-65) patients when compared to age group among 26-45 patients. In this study, we confirmed that Buccal Mucosa patients were found to be with high frequency of Arginine when compared with proline. According to the 1997 TNM staging system, 60 patients presented with stage IV, and 47 with stage III disease. For patients with stage IV disease, frequencies of the Arg/Arg, Arg/ Pro and Pro/Pro genotypes were 30.6%, 25.0% and 45.45%, respectively. For patients with stage III disease, the frequencies of the Arg/Arg, Arg/Pro and Pro/Pro genotypes were 39.7%, 50.0% and 22.7%, respectively. We observed that stage 3 and stage 4 patients with high frequency of *p53* codon 72 polymorphism. Our study between the *p53* genotypes and habitual risk factors like chewing and smoking confessed that the frequency of Arg/Arg (OR: 1.01, 95% CI: 0.31-3.68) Arg/Pro, (OR: 1.40, 95% CI: 0.27-7.13) & Pro/Pro (OR: 2.75, 95% CI: 0.31-24.1) genotype were high in chewers than smokers. Arginine allele frequency was detected to be high (OR: 1.04, 95% CI: 0.34-3.21) in alcohol+chewing patients when compared to alcohol+smoking patients. However, the interaction between *p53* genotypes and age, site of diagnosis, tumor stage, and habitual risk factors was not statistically significant (Table 3).

Discussion

Cancer is a multi-step mechanism occurring as an effect of series of progressive genetic alterations. Molecular genetic studies revealed that a group of tumor suppressor gene and proto-oncogene alterations were effective in cancer formation. *p53* is the most important tumor suppressor gene which is effective in different cancers including oral squamous cell carcinoma. Detection of *p53* mutations is an important factor in prognosis and early diagnosis.

Recently, several studies have provided evidence that *p53* polymorphism at codon 72 may be associated with certain tumors, such as esophageal, lung cancer [14], hepatocellular carcinoma [15] and breast cancer [16]. In particular, both Arg and Pro alleles have been shown to be associated with a high risk of malignancy. This study evaluates the association between the risk of developing oral squamous

P53 Genotyping	Cases (n = 150)	Controls (n = 150)	Odds Ratio	95% CI	P-Value
Arg	216 (72%)	267 (89%)	0.31	0.20-0.49	< 0.0001
Pro	84 (28%)	33 (11%)	3.1	2.02-4.88	< 0.0001
Arg/Arg	88 (58.66%)	124 (82.66%)	0.29	0.17-0.50	0.0001
Arg/Pro	40 (26.66%)	19 (12.66%)	2.50	1.37-4.57	0.002
Pro/Pro	22 (14.66%)	7 (4.66%)	3.51	1.45-8.49	0.005

p = < 0.05 (Significant) OR: Odds Ratio, 95% Confidential Intervals, Chi Square.

Table 2: Distribution of *p53* genotypes/alleles in OSCC patients and controls.

P53 **Genotyping**	**Males (n = 81)**	**Females (n = 69)**	**Statistics**
Arg/Arg	46	42	OR: 0.84, 95% CI: 0.43-1.62, P = 0.61
Arg/Pro	22	18	OR: 1.05, 95% CI: 0.51-2.18, P = 0.88
Pro/Pro	13	9	OR: 1.27, 95% CI: 0.50-3.19, P = 0.60
P53 **Genotyping**	**Age Between 26-45 (n = 48)**	**Age Between 46-65 (n = 81)/ Above 66**	**Statistics**
Arg/Arg	29	46 / 11	OR: 1.16, 95% CI: 0.56-2.40, P = 0.68
Arg/Pro	12	21 / 7	OR: 0.95, 95% CI: 0.41-2.16, P = 0.90
Pro/Pro	7	14 / 1	OR: 0.81, 95% CI: 0.30-2.19, P = 0.68
P53 **Genotyping**	**BM (n = 56)**	**Tongue (n = 33)**	**Statistics**
Arg/Arg	33	19	OR: 1.05, 95% CI: 0.44-2.52, P = 0.90
Arg/Pro	15	7	OR: 1.35, 95% CI: 0.48-3.77, P = 0.55
Pro/Pro	8	7	OR: 1.61, 95% CI: 0.20-2.19, P = 0.40
P53 **Genotyping**	**Stage IV (n = 47)**	**Stage III (n = 60)**	**Statistics**
Arg/Arg	35	27	OR: 1.03, 95% CI: 0.47-2.24, P = 0.92
Arg/Pro	20	10	OR: 1.85, 95% CI: 0.76-4.46, P = 0.17
Pro/Pro	5	10	OR: 3.70, 95% CI: 0.89-15.3, P = 0.07
P53 **Genotyping**	**Chewing (n = 46)**	**Smoking (n = 12)**	**Statistics**
Arg/Arg	27	7	OR: 1.01, 95% CI: 0.31-3.68, P = 0.98
Arg/Pro	9	4	OR: 1.40, 95% CI: 0.27-7.13, P = 0.68
Pro/Pro	10	1	OR: 2.75, 95% CI: 0.31-24.1, P = 0.36
P53 **Genotyping**	**Alcohol/Chewing (n = 35)**	**Alcohol/Smoking (n = 19)**	**Statistics**
Arg/Arg	17	9	OR: 1.04, 95% CI: 0.34-3.21, P = 0.93
Arg/Pro	13	6	OR: 1.28, 95% CI: 0.39-4.19, P = 0.68
Pro/Pro	5	4	OR: 0.62, 95% CI: 0.14-2.67, P = 0.52

Table 3: Association between TP53 codon 72 status and clinicopathological characteristics.

cell carcinoma and the genotype at codon 72 of the *p53* gene. The Arg/Arg genotype was more in controls than cases, whereas according to the previous reports, general populations from Asia exhibit high frequencies of the Pro allele compared to the Arg one, while lower prevalence of Pro are found in populations. In our study, Arg allele showed higher frequency than Pro allele in both cancer and control group. Previous studies have investigated the association of this polymorphism with oral cancer, those studies have reported an increased risk of oral cancer development in the presence of Arg/Arg compared to those with Pro/Pro in Taiwan [17] and Germany population [18]. The arginine variant was reported to be more efficient than the proline variant at inducing apoptosis due to the varied tendency of protein localization in the mitochondria [19]. Homozygous arginine at codon 72 appears to play no role in the development of oral cancer and also it cannot serve as a biomarker for early identification of oral cancer [20]. The present study also found that subjects with Arg/Pro and Pro/Pro had a 2.50 and 3.51-fold increased risk of developing oral squamous cell carcinoma cancer, suggesting a strong association of both Arg/Pro and Pro/Pro of codon 72 of the *p53* polymorphism with tumor progression in south Indian population. To our knowledge, our study is the first to show a significant association between *p53* codon 72 polymorphism and oral squamous cell carcinoma. Several studies showed that the proline variant more efficiently activated TP53-dependent DNA repair-related genes in different cell based assays. Moreover, the Pro72 variant-bearing cells also exhibited reduced micronuclei formation, suggesting that it promoted greater genomic stability [21]. Previous Meta-analysis study reported that the TP53 Pro/Pro polymorphism significantly increase susceptibility to NPC [22]. Marin et al. [23], reported that the proline variant is more effective for inducing G1 arrest than the other variant, probably due to altered binding affinity to p73.

The effect of *p53* codon 72 polymorphism on the function of *p53* protein remains unclear. However, functional differences of these variants of *p53* protein encoded by different genotypes have been studied. *P53* protein with Pro is structurally different from *p53* with Arg, which is reflected by its altered electrophoretic mobility. *p53* codon 72 polymorphism may influence expression of *p53* gene, which encodes a nucleoprotein functioning as a transcription factor that regulates cell cycle-related genes [24]. Tumors having the Arg72 constitution showed lack of co-expression of Fas and FasL and high expression of Bcl2 proteins, which was associated with impairment or lack of apoptosis. The expression of these proteins was reversed in tumors having the Pro72 constitution and this was associated with improvement of apoptosis induction. In heterozygous Arg/Pro tumors, the Arg allele seems to prevent apoptosis. Thus, there was a significant correlation between codon 72 genotype and apoptosis induction [25]. The arginine (Arg72) allele increases the ability of *p53* to locate to mitochondria and induce cellular death, whereas proline allele (Pro 72) exhibits a lower apoptotic potential and an increased cellular arrest in G1 of the cell cycle [7].

Oral cancers occur in patients with tumors arising from the gingival, tongue, hard palate, and lip. However, previous studies of specific types of head and neck cancers usually found positive association with *p53* codon 72 polymorphism, such as nasopharyngeal carcinoma

[26] and laryngeal tumors [27]. In the present study, Buccal Mucosa patients showed high frequency of *p53* codon 72 polymorphism. Tobacco contains 2000 chemicals many of which are have been directly related to causing cancer. *p53* mutations commonly arise as a result of alcohol and tobacco exposure, and their presence is associated with the early recurrence and development of second primary tumors [28]. We revealed that delayed stage patients with pro allele showed high frequency with the effect of chewing when compared to smoking. The relationship between age, gender & habitual risk factors are not statistically significant with *p53* codon 72 polymorphism in south Indian population.

Conclusion

In conclusion, codon 72 polymorphism were thought to function distinctly from one another and their expression levels also modulated cancer risk. The findings of the present study indicate that *p53* codon 72 polymorphism may be a genetic predisposing factor for oral squamous cell carcinoma and *p53* Arg72 protein may be correlated with possible increased risk of this kind of cancers in south Indian population.

References

1. Sunny L, Yeole BB, Hakama M, Shiri R, Sastry PS, et al. (2004) Oral cancers in Mumbai, India: a fifteen years perspective with respect to incidence trend and cumulative risk. Asian Pac J Cancer Prev 5: 294-300.
2. Lane DP (1992) Cancer. p53, guardian of the genome. Nature 358: 15-16.
3. Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88: 323-331.
4. Matakidou A, Eisen T, Houlston RS (2003) TP53 polymorphisms and lung cancer risk: a systematic review and meta-analysis. Mutagenesis 18: 377-385.
5. Buchman VL, Chumakov PM, Ninkina NN, Samarina OP, Georgiev GP (1988) A variation in the structure of the protein-coding region of the human p53 gene. Gene 70: 245-252.
6. Thomas M, Kalita A, Labrecque S, Pim D, Banks L, et al. (1999) Two polymorphic variants of wild-type p53 differ biochemically and biologically. Mol Cell Biol 19: 1092-1100.
7. Bergamaschi G, Merante S, Orlandi E, Galli A, Bernasconi P, et al. (2004) TP53 codon 72 polymorphism in patients with chronic myeloid leukemia. Haematologica 89: 868-869.
8. Sreeja L, Syamala V, Raveendran PB, Santhi S, Madhavan J, et al. (2008) p53 Arg72Pro polymorphism predicts survival outcome in lung cancer patients in Indian population. Cancer Invest 26: 41-46.
9. De Chaudhuri S, Kundu M, Banerjee M, Jayanta K (2006) Previously we have reported that the p53 codon 72 arginine (Arg) homozygous genotype cancer through drinking water. Int. J. Cancer 118.
10. Rajkumar T, Samson M, Rama R, Sridevi V, Mahji U, et al. (2008) TGFbeta1 (Leu10Pro), p53 (Arg72Pro) can predict for increased risk for breast cancer in south Indian women and TGFbeta1 Pro (Leu10Pro) allele predicts response to neo-adjuvant chemo-radiotherapy. Breast Cancer Res Treat 112: 81-87.
11. Sailaja K, Surekha D, Nageswara Rao D, Raghunadha Rao D, Balakrishna B, et al. (2009) TP53 Codon 72 polymorphism and risk of chronic myeloid leukemia. Gene Ther Mol Biol 13: 316-320.
12. Tandle AT, Sanghvi V, Saranath D (2001) Determination of p53 genotypes in oral cancer patients from India. Br J Cancer 84: 739-742.
13. Alluri RV, Mohan V, Komandur S, Chawda K, Chaudhary JR, et al. (2005) MTHFR C677T gene mutation as a risk factor for arterial stroke: a hospital based study. Eur J Neurol 12: 40-44.
14. Fan R, Wu MT, Miller D, Wain JC, Kelsey KT, et al. (2000) The p53 codon 72 polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev 9: 1037-1042.
15. Yu MW, Yang SY, Chiu YH, Chiang YC, Liaw YF, et al. (1999) A p53 genetic polymorphism as a modulator of hepatocellular carcinoma risk in relation to chronic liver disease, familial tendency, and cigarette smoking in hepatitis B carriers. Hepatology 29: 697-702.
16. Sjalander A, Birgander R, Hallmans G, Cajander S, Lenner P, et al. (1996) p53 polymorphisms and haplotypes in breast cancer, Carcinogenesis 17: 1313-1316.
17. Bau DT, Tsai MH, Lo YL, Hsu CM, Tsai Y, et al. (2007) Association of p53 and p21(CDKN1A/WAF1/CIP1) Polymorphisms with Oral Cancer in Taiwan Patients. Anticancer Res 27: 1559-1564.
18. Brant O, Hoffmann M, Kanappilly A, Görögh T, Gottschlich S, et al. (2007) P53 codon 72 polymorphism in squamous cell carcinoma of the head and neck region. Anticancer Res 27: 3301-3305.
19. 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.
20. Katiyar S, Thelma BK, Murthy NS, Hedau S, Jain N, et al. (2003) Polymorphism of the p53 codon 72 Arg/Pro and the risk of HPV type 16/18-associated cervical and oral cancer in India. Mol Cell Biochem 252: 117-124.
21. Siddique M, Sabapathy K (2006) Trp53-dependent DNA-repair is affected by the codon 72 polymorphism. Oncogene 25: 3489-3500.
22. Zhuo XL, Cai L, Xiang ZL, Zhuo WL, Wang Y, et al. (2009) TP53 codon 72 polymorphism contributes to nasopharyngeal cancer susceptibility: a meta-analysis. Arch Med Res 40: 299-305.
23. Marin MC, Jost CA, Brooks LA, Irwin MS, O'Nions J, et al. (2000) A common polymorphism acts as an intragenic modifier of mutant p53 behaviour. Nat Genet 25: 47-54.
24. Gottlieb TM, Oren M (1996) p53 in growth control and neoplasia. Biochim Biophys Acta 1287: 77-102.
25. Schneider-Stock R, Mawrin C, Motsch C, Boltze C, Peters B, et al. (2004) Retention of the arginine allele in codon 72 of the p53 gene correlates with poor apoptosis in head and neck cancer. Am J Pathol 164: 1233-1241.
26. Tsai MH, Lin CD, Hsieh YY, Chang FC, Tsai FJ, et al. (2002) Prognostic significance of the proline form of p53 codon 72 polymorphism in nasopharyngeal carcinoma. Laryngoscope 112: 116-119.
27. Sourvinos G, Rizos E, Spandidos DA (2001) p53 codon 72 polymorphism is linked to the development and not the progression of benign and malignant laryngeal tumors. Oral Oncol 37: 572-578.
28. Shin DM, Lee JS, Lippman SM, Lee JJ, Tu ZN, et al. (1996) p53 expressions: predicting recurrence and second primary tumors in head and neck squamous cell carcinoma. J Natl Cancer Inst 88: 519-529.