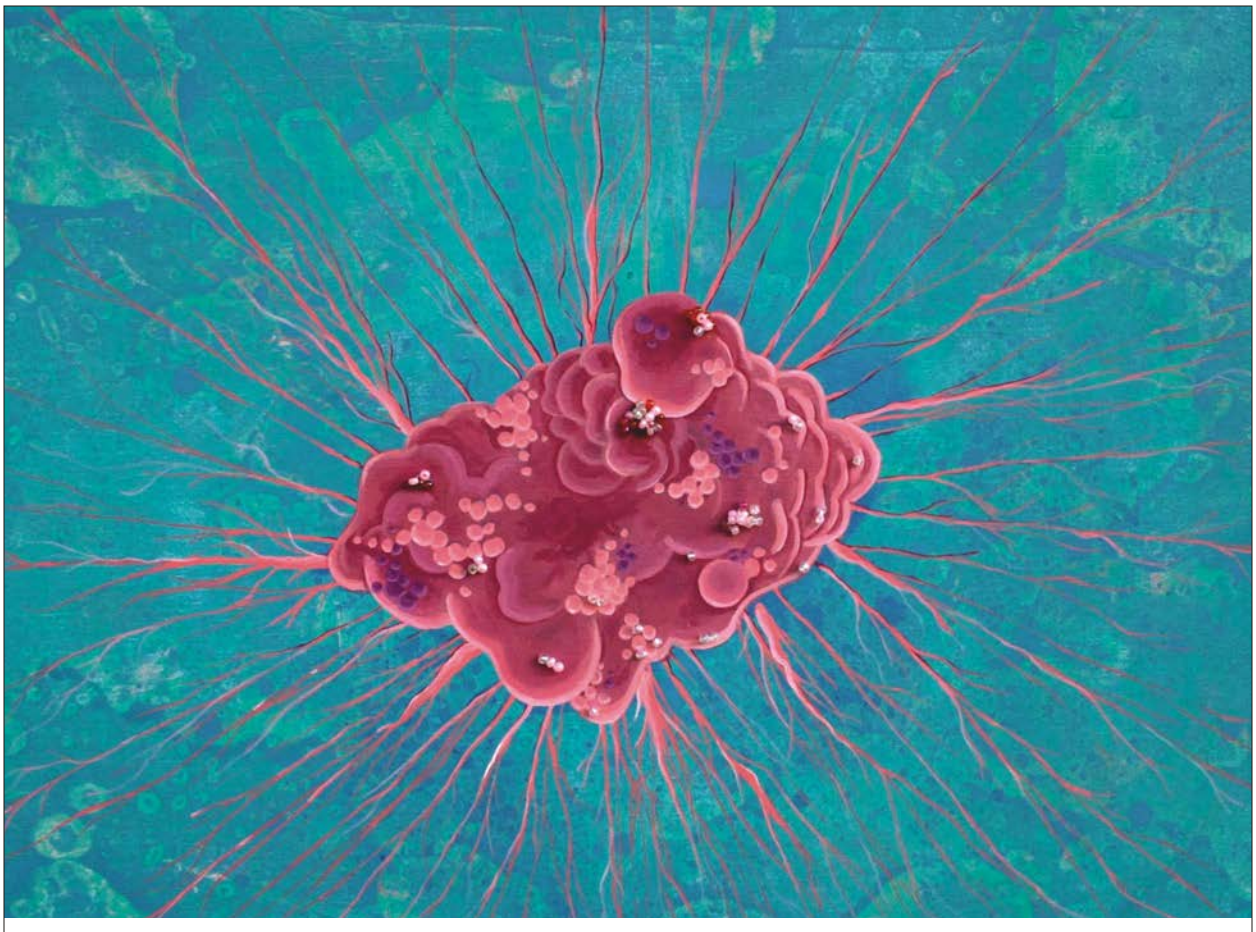

International Journal of Cancer Research

ISSN 1811-9727

Academic Journals Inc.

www.academicjournals.com

International Journal of Cancer Research 9 (1): 1-8, 2013
ISSN 1811-9727 / DOI: 10.3923/ijcr.2013.1.8

The p.Pro47Ser Polymorphism of *TP53*: A Systematic Review

[1]Neha Chandel, [2]Ashish Chauhan and [2]Kamlesh Guleria
[1]Guru Nanak Dev University, Punjab, India
[2]National Institute of Pharmaceutical Education and Research, Punjab, India

Corresponding Author: Neha Chandel, Guru Nanak Dev University, Punjab, India

ABSTRACT

The tumor suppressor gene *TP53* rs1800371 polymorphism (g.11370 C>T, c.139C>T, p.Pro47Ser) has been extensively investigated as a potential risk factor for different types of cancers and many diseases, but the results have been inconclusive. After searching multiple electronic databases to investigate the association between the p.Pro47Ser polymorphism and disease susceptibility, the present study has identified eleven eligible case-control studies, after investigating 2,502 cases and 3,740 controls. Also, four case-studies were included, investigating 225 cases. The genotypic frequency of Pro/Pro genotype in all the case-control studies was 100% (approximately). That led to conclude that there is no association between *TP53* rs1800371 polymorphism and disease susceptibility. Published results seem to be driven by technical artifacts rather than justified biological effects. In order to determine the potential clinical implications of this polymorphism, future genetic association studies should use more rigorous genotyping methods and avoid the use of tumor tissue as a source of DNA to prevent genotype misclassification due to loss of heterozygosity.

Key words: Polymerase chain reaction, restriction fragment length polymorphism, single strand conformation polymorphism, proline, serine

INTRODUCTION

TP53, a tumor suppressor gene (OMIM, 191170) localized on 17p13. It consists of 11 exons spanning 20 kbp resulting in a transcript of 2629 bp which encodes for p53, a nuclear phosphoprotein of 393 amino acids and 53 kD (McBride *et al*., 1986; Levine, 1997). The p53 protein is comprised of multiple functional domains with an acidic N-terminus containing activation domain which serves as a transcriptional activator, a hydrophobic central DNA Binding Domain (DBD) which binds to specific DNA sequences (repeats of the consensus RRRCA/TA/TGYYY) within regulatory regions of target genes and a basic C-terminus which contains tetramerization domain and multiple nuclear localization sequences as well as multiple lysine residues which are key to regulating p53 activity (Hainaut and Hollstein, 2000). *TP53* is mutated in 50-70% of human sporadic cancers (Hollstein *et al*., 1991; Levine, 1997). Approximately, 85 polymorphisms and 27580 somatic mutations are known in the *TP53* (Petitjean *et al*., 2007). Predisposition to several human cancers and other diseases has been associated with genetic polymorphisms, which may represent an important contribution to disease susceptibility.

Many genetic alterations like mutations and polymorphisms results in dysfunctioning and inactivation of p53 leading to cancer development and many other diseases. Several polymorphisms

have been identified within the *TP53*, both in non-coding and coding regions (Murphy, 2006; Bojesen and Nordestgaard, 2008; Costa *et al*., 2008; Whibley *et al*., 2009). Most of these polymorphisms are single-nucleotide polymorphisms (SNPs) affecting a single base. The extensively studied polymorphisms of *TP53* in exon 4 are codon 72 (rs1042522) and codon 47 (rs1800371) as these polymorphisms leads to an amino acid change. On codon 72, there is a change from Arginine (A) to Proline (P) whereas, on codon 47, there is a change from Proline (P) to Serine (S).

p.Pro47Ser (rs1800371) is a rare polymorphism in the N-terminal transactivation domain of p53. The N-terminal domain of p53 undergoes phosphorylation which regulates its transactivation properties (Dumaz and Meck, 1999; Chao *et al*., 2003; Kruse and Gu, 2008). Serine 46 phosphorylation plays an important role in p53-dependent apoptosis which has been demonstrated by several groups (Bulavin *et al*., 1999; Oda *et al*., 2000; Sanchez-Prieto *et al*., 2000; Takekawa *et al*., 2000; Okamura *et al*., 2001). Li *et al*. (2005) reported that Ser46 is phosphorylated by p38 and homeodomain-interacting protein kinase 2 (HIPK2), which enhances the transcription of apoptosis-related genes and hence promotes p53-mediated apoptosis. These kinases are directed to phosphorylation sites by a proline residue adjacent to Ser46 and thus, replacement of proline at 47, as occurs with the p.Pro47Ser polymorphism, leads to decreased phosphorylation at Ser46. This reduced phosphorylation at Ser46 results in decreased induction of the pro-apoptotic genes p53AIP1 (p53-regulated apoptosis-inducing protein 1) and BBC3 and decreased apoptosis in human cell lines transfected with the Ser47 variant (Li *et al*., 2005). Therefore, the Ser47 polymorphism would be predicted to impair phosphorylation on serine 46 as occurs with the p.Pro47Ser polymorphism, decrease transactivation of pro-apoptotic target genes and thus potentially increase cancer risk (Feng *et al*., 2006; Kurihara *et al*., 2007). Several epidemiologic studies have addressed the influence of this polymorphism on cancer risk and many other diseases; however, small sample sizes and deficiencies in study design have contributed to conflicting results. To propose a comprehensive evaluation of the potential association of this polymorphism with disease susceptibility, we conducted a systematic study and meta-analysis of candidate genetic association studies that still remains unexplored.

TP53 GENE POLYMORPHISM

Many scientists have explored various aspects of science, health, diseases and obtained productive results (Abdi *et al*., 2010; Abd El-Hady, 2011; Abd El-Hady *et al*., 2011; Raja and Thilagavathi, 2011; Issaoui *et al*., 2011; Das *et al*., 2011; Rocco, 2011, Aan *et al*., 2011; Adedayo, 2012; Chauhan and Kaith, 2012) yet a lot remains unexplored in the field of biosciences including genetics. To identify genetic association studies published before July 4, 2012, investigating the association between the rs1800371 polymorphism located within the *TP53* gene, using computer-based searches (last search: July 3, 2012) of MEDLINE (PubMed), the Human Genome Epidemiology Network (HuGE Net) Literature Finder and the NIH Genetic Association Database, using keywords related to the *TP53* gene and polymorphisms (the full search strategy is available from the authors on request). Additionally, we searched two *TP53*-specific databases that collect information related to *TP53* polymorphisms: the IARC *TP53* database and the p53 website (Fig. 1). We also hand-searched the reference lists for all retrieved studies and relevant review articles, as well as journals known to publish studies relevant to the topic. Studies using an analytic design (case-control, nested case-control, or cohort) and employing validated genotyping methods to examine the frequency of rs1800371 among patients and controls were eligible for inclusion. Family-based studies were not considered eligible owing to different design

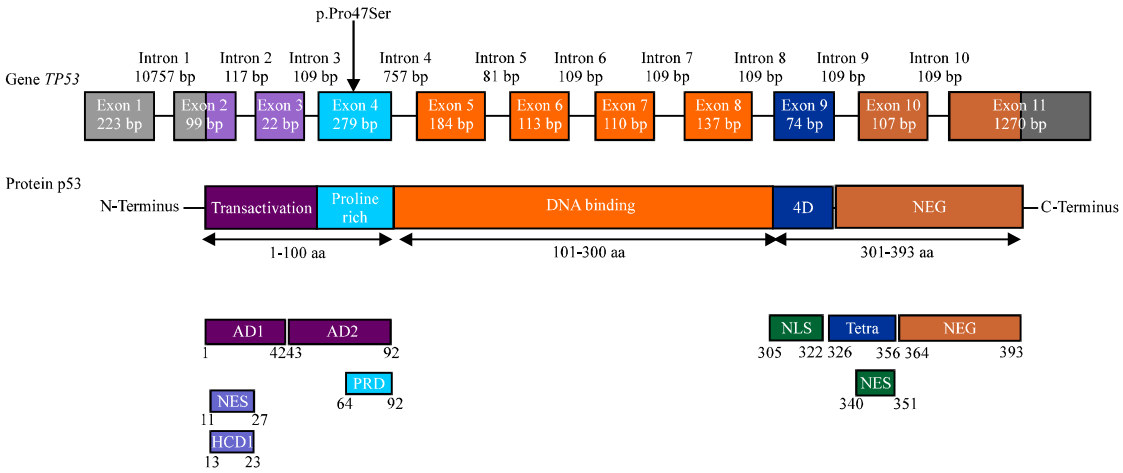

Fig. 1: Organization of *TP53* and p53 protein, The amino-terminus of p53 contains AD1 (activation domain 1), AD2 (activation domain 2), PRD (proline rich domain), NES (nuclear exclusion domain) and HCD I (highly conserved domain I), The carboxy-terminus of p53 contains tetra (4D) (oligomerization domain), NEG (negative regulation domain), NES (nuclear exclusion domain) and NLS (nuclear localization domain), The grayish part of exon 1, 2 and 11 are UTR (un-translated regions) regions

considerations. We considered studies published in all languages. The following information was abstracted from each study: First author, journal, year of publication, study design, matching, ethnicity of participants, definition and numbers of cases and controls, DNA extraction and genotyping methods, source of genetic material for genotyping cases, frequency of genotypes and the number of cases and controls for each *TP53* genotype (Table 1).

Other studies which investigated this polymorphism are as follows. Fifty four thin prep-processed fine needle breast aspirates and 31 surgical specimens were used for detection of *TP53* alterations. The investigators detected codon 47 polymorphism in one aspirant and concluded that DNA suitable for analysis of *TP53* sequence changes can be extracted from thin prep-processed breast fine-needle aspirates (Pollett *et al.*, 2000). Eighty five Canadian children diagnosed with a sporadic malignant central nervous system tumor were investigated for the presence of *TP53* sequence alterations in exon 4 (p.P47S and p.R72P) and exon 6 (p.R213R) using PCR-SSCP analysis and direct sequencing. No association was found between p.Pro47Ser polymorphism and central nervous system tumor (Portwine *et al.*, 2001). Two hundred African American cancer patients were studied for the p.Pro47Ser polymorphism of *TP53* using genotyping analysis was performed, GST Fusion proteins and p38 MAPK, HIPK2 Kinase assays and Apoptosis Assay (TUNEL analysis and multi caspase assay). The authors observed that Ser47 polymorphism might play an important role in cancer risk, progression and the efficacy of therapy (Li *et al.*, 2005). Seventy eight Brazilian renal transplant recipients and 151 controls were studied for p.Pro47Ser polymorphism of *TP53* and the susceptibility to herpes virus type 6 (HHV6) and herpes virus type 1 (HHV1) infection in renal transplant recipients. The authors suggested that genotyping of p.Pro47Ser polymorphism of *TP53* might not be useful in screening for patients at higher risk for post-transplant infections (Leite *et al.*, 2006). Ninety four Brazilian bladder cancer patients (76 males and 18 females) and 159 healthy controls (104 males and 55 females) were investigated

Table 1: Characteristics of eligible studies

				Patients						Controls						
				P/P		P/S		S/S		P/P		P/S		S/S		
Disease	Population	Genotyping method	Source of DNA in cases	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	References
Lung cancer	American African and Caucasians	PCR-RFLP	Blood	98	90.6	3	9.37	0	0	-	-	-	-	-	-	Felley-Bosco *et al.* (1993)
Lung cancer	-	PCR-SSCP	Skin fibro-blasts	64	100	0	0	0	0	-	-	-	-	-	-	Auer *et al.* (1999)
Cancer	America	PCR-RFLP, Electrospray lonization Quadruple mass Spectroscopy	Human Foreskin fibroblast	10	100	0	0	0	0	-	-	-	-	-	-	Walters *et al.* (2001)
Primary breast tumor	White and African Brazilian	PCR-SSCP, Direct DNA sequencing	Blood	48	96	0	0	2	4	-	-	0	-	-	-	Nagai *et al.* (2003)
Schizo-phrenia	Chinese	PCR-RFLP	Blood	701	100	0	0	0	0	695	100	0	0	0	0	Yang *et al.* (2004)
Neural Tube Defect	Ireland	PCR-RFLP, Single variant analysis and haplotype analysis	Blood	549	100	0	0	0	0	999	100	0	0	0	0	Pangilinan *et al.* (2008)
Gliomas	Southeast Brazil	PCR-RFLP	Blood	91	96.8	3	3.2	0	0	98	98	2	2	0	0	Pinto *et al.* (2008)
Papillary thyroid Cancer	Saudi Arabia	PCR-RFLP	Blood	223	100	0	0	0	0	229	100	0	0	0	0	Siraj *et al.* (2008)
Juvenile Chronic and Rheuma-toid Arthritis	Germany	PCR-RFLP, Western blot	Blood	31	100	0	0	0	0	885	100	0	0	0	0	Taubert *et al.* (2008)
Extra-Axial Brain Tumors	Brazil	PCR-RFLP, Methylation-specific PCR	Blood	66	73.3	24	26.7	0	0	98	98	2	2	0	0	Almeida *et al.* (2009)
Primary open Angle glaucoma	West Virginia	PCR-RFLP, Sequence analysis	Blood	191	100	0	0	0	0	167	100	0	0	0	0	Daugherty *et al.* (2009)
Colorectal Cancer	Kashmir	PCR-RFLP	Blood	81	94.2	0	0	5	5.8	156	97.5	0	0	4	2.5	Sameer *et al.* (2010)
Breast Cancer	Arab	PCR-RFLP	Blood	226	99.6	1	(0.4	0	0	105	100	0	0	0	0	Alawadi *et al.* (2011)
Urinary Bladder Cancer	North India	PCR-RFLP	Blood	181	90.5	12	6.0	7	3.5	176	88.0	7	3.5	17	8.5	Jaiswal *et al.* (2011)
Breast Cancer	Saudi Arabia	Direct sequencing	Breast cancer tissues	100	100	0	0	0	0	100	0	0	0	0	0	Al-Qasem *et al.* (2012)

for p.Pro47Ser polymorphism of *TP53* using univariate logistic regression analysis and multivariate regression analysis. The investigators concluded that the effect of *TP53* p.Pro47Ser is not associated with susceptibility to bladder cancer (Santos *et al*., 2011).

META-ANALYSIS OF GENETIC ASSOCIATION STUDIES

Our initial search identified many studies, of which few were considered potentially eligible for inclusion in this review and were retrieved in full text and some as abstracts. Of those, 20 were considered eligible for the meta-analysis (references to excluded studies are available on request). The first was published in 1993 and the last in 2012. Detailed study characteristics are presented in Table 1. These twenty studies include fifteen studies on different types of cancer and five studies on other diseases. The investigated cancer cases in four case studies were 225, respectively and in seven case-control studies, the number of cases and controls were 6,514 and 9,334, respectively. In another four case-control studies which were on different diseases (schizophrenia, neural tube defect, juvenile chronic and rheumatoid arthritis and primary open angle glaucoma), the number of cases and controls investigated were 1,472 and 2,746, respectively. Age and gender matched unrelated healthy individuals were taken in all the eleven case-control studies. Of these twenty studies, eighteen studies showed no association of p.Pro47Ser polymorphism with disease susceptibility whereas studies by Li *et al*. (2005) on cancer and Almeida *et al*. (2009) on extra-axial brain tumors showed that this polymorphism is associated with cancer risk, progression and the efficacy of therapy.

CONCLUSION

This systematic review and meta-analysis of genetic association studies shows that *TP53* p.Pro47Ser is unlikely to be a major risk factor for different types of cancers and many diseases. Several sources of bias, including the use of inappropriate genotyping material and the lack of quality control, need to be addressed in the design of future studies to determine the potential clinical implications of this polymorphism in pathogenesis of cancer and other disease. Also, future genetic association studies should use more rigorous genotyping methods and avoid the use of tumor tissue as a source of DNA to prevent genotype misclassification due to loss of heterozygosity.

REFERENCES

Aan, M.P.S., M. Krishna, H.N.N. Murthy and S.K. Rai, 2011. Thermal, mechanical, morphological and flame retardance properties of DABA modified novolac/CFRP composites. Asian J. Mater. Sci., 3: 20-30.

Abd El-Hady, R.A.M., 2011. The effect of aesthetic beauty design on the performance properties of jacquard weft knitted fabrics. Asian J. Textile, 1: 74-86.

Abd El-Hady, R.A.M. and R.A.A. Abd El-Baky, 2011. Enhancing the functional properties of sportswear fabric based carbon fiber. Asian J. Text., 1: 14-26.

Abdi, S., Y. Ourova and O. Menchi, 2010. Development and characterization of metal matrix composite steel/Cu-Zn. Asian J. Mater. Sci., 2: 147-153.

Adedayo, A.V., 2012. Factors influencing semi-solid microsctructure. Asian J. Mater. Sci., 4: 1-12.

Al-Qasem, A., M. Toulimat, A. Tulbah, N. Elkum, T. Al-Tweigeri and A. Aboussekhra, 2012. The p53 codon 72 polymorphism is associated with the risk and early onset of breast cancer among Saudi women. Oncol. Lett., 3: 875-878.

Alawadi, S., L. Ghabreau, M. Alsaleh, Z. Abdulaziz, M. Rafeek, N. Akil and M. Alkhalaf, 2011. P53 gene polymorphisms and breast cancer risk in Arab women. Med. Oncol., 28: 709-715.

Almeida, L.O., A.C. Custodio, G.R. Pinto, M.J. Santos and J.R.W. Almeida *et al.*, 2009. Polymorphisms and DNA methylation of gene TP53 associated with extra-axial brain tumors. Genet. Mol. Res., 8: 8-18.

Auer, H., K. Warncke, D. Nowak, F. Koops, U. Jaeger, R. Kurzbauer and H.W. Ruediger, 1999. Variations of p53 in cultured fibroblasts of patients with lung cancer who have a presumed genetic predisposition. Am. J. Clin. Oncol., 22: 278-282.

Bojesen, S.E. and B.G. Nordestgaard, 2008. The common germline Arg72Pro polymorphism of p53 and increased TP53 Pro47Ser and Arg72Pro polymorphisms and colorectal cancer in humans. Cell Cycle, 7: 158-163.

Bulavin, D.V., S. Saito, M.C. Hollander, K. Sakaguchi, C.W. Anderson, E. Appella and A.J. Fornace Jr., 1999. Phosphorylation of human p53 by p38 kinase coordinates N-terminal phosphorylation and apoptosis in response to UV radiation. EMBO J., 18: 6845-6854.

Chao, C., M. Hergenhahn, M.D. Kaesen, Z. Wu and S. Saito *et al.*, 2003. Cell type and promoter-specific roles of Ser18 phosphorylation in regulating p53 responses. J. Biol. Chem., 278: 41028-41033.

Chauhan, A. and B. Kaith, 2012. Sorrel fiber as reinforcement in bio-composite. J. Environ. Sci. Technol., 5: 343-353.

Costa, S., D. Pinto, D. Pereira, H. Rodrigues, J. Cameselle-Teijeiro, R. Medeiros and F. Schmitt, 2008. Importance of TP53 codon 72 and intron 3 duplication 16bp polymorphisms in prediction of susceptibility on breast cancer. BMC Cancer, Vol. 8. 10.1186/1471-2407-8-32

Das, B.R., S.M. Istiaque and R.S. Rengasamy, 2011. Migration behavior of polyester/viscose blended rotar spun yarns. Asian J. Tex., 1: 27-34.

Daugherty, C.L., H. Curtis, T. Realini, J.F. Charlton and S. Zareparsi, 2009. Primary open angle glaucoma in a Caucasian population is associated with the p53 codon 72 polymorphism. Mol. Vis., 15: 1939-1944.

Dumaz, N. and D.W. Meek, 1999. Serine 15 phosphorylation stimulates p53 transactivation but does not directly influence interaction with HDM2. EMBO J., 18: 7002-7010.

Felley-Bosco, E., A. Weston, H.M. Cawley, W.P. Bennett and C.C. Harris, 1993. Functional studies of a germ-line polymorphism at codon 47 within the p53 gene. Am. J. Hum. Genet., 53: 752-759.

Feng, L., M. Hollstein and Y. Xu, 2006. Ser46 phosphorylation regulates p53-dependent apoptosis and replicative senescence. Cell Cycle, 5: 2812-2819.

Hainaut, P. and M. Hollstein, 2000. P53 and human cancer: The first ten thousand mutations. Adv. Cancer Res., 77: 81-137.

Hollstein, M., D. Sidransky, B. Vogelstein and C.C. Harris, 1991. P53 mutations in human cancers. Science, 253: 49-53.

Issaoui, C., A.H. Said and S. Roudesli, 2011. A polyanizidine coated textile: Elaboration and characterization. Asian J. Textile, 1: 98-105.

Jaiswal, P.K., A. Goel and R.D. Mittal, 2011. Association of p53 codon 248 (exon7) with urinary bladder cancer risk in the North Indian population. Biosci. Trends, 5: 205-210.

Kruse, J. P. and W. Gu, 2008. SnapShot: P53 posttranslational modifications. Cell, 133: 930-930.

Kurihara, A., H. Nagoshi, M. Yabuki, R. Okuyama, M. Obinata and S. Ikawa, 2007. Ser46 phosphorylation of p53 is not always sufficient to induce apoptosis: Multiple mechanisms of regulation of p53-dependent apoptosis. Genes Cells, 12: 853-861.

Leite, J.L., J.A. Manfrinatto, M. Mazzali and L.S. Ward, 2006. Polymorphisms at exon 4 of p53 and the susceptibility to herpesvirus types 6 and 1 infection in renal transplant recipients. Transpl. Int. 19: 732-737.

Levine, A.J., 1997. P53, the cellular gatekeeper for growth and devision. Cell, 88: 323-331.

Li, X., P. Dumont, A.D. Pietra, C. Shetler and M.E. Murphy, 2005. The codon 47 polymorphism in p53 is functionally significant. J. Biol. Chem., 280: 24245-24251.

McBride, O.W., D. Merry and D. Givol, 1986. The gene for human p53 cellular tumor antigen is located on chromosome 17 short arm (17p13). Proc. Natl. Acad. Sci., 83: 130-134.

Murphy, M.E., 2006. Polymorphic variants in the p53 pathway. Cell Death Differ., 13: 916-920.

Nagai, M.A., H.S. Barbosa, M.A. Zago, W.A. Silva and I.N. Nishimoto *et al.*, 2003. TP53 mutations in primary breast carcinomas from white and African-Brazilian patients. Int. J. Oncol., 23: 189-196.

Oda, K., H. Arakawa, T. Tanaka, K. Matsuda and C. Tanikawa *et al.*, 2000. p53 AIP1, a potential mediator of p53-dependent apoptosis and its regulation by Ser-46-phosphorylated p53. Cell, 102: 849-862.

Okamura, S., H. Arakawa, T. Tanaka, H. Nakanishi and C.C. Ng *et al.*, 2001. p53DINP1, a p53-inducible gene, regulates p53-dependent apoptosis. Mol. Cell, 8: 85-94.

Pangilinan, F., K. Geiler, J. Dolle, J. Troendle and D.A. Swanson *et al.*, 2008. Construction of high resolution linkage disequilibrium map to evaluate common gene-tic variation in TP53 and neural tube defect risk in an Irish population. Am. J. Med. Genet., 146: 2617-2625.

Petitjean, A., E. Mathe, S. Kato, C. Ishioka and S.V. Tavtigian *et al.*, 2007. Impact of mutant p53 functional properties on *TP53* mutation patterns and tumor phenotype: Lessons from recent developments in the IARC *TP53* database. Human Mutat., 28: 622-629.

Pinto, G.R., F.K. Yoshioka, R.L. Silva, C.A. Clara and M.J. Santos *et al.*, 2008. Prognostic value of TP53 Pro47Ser and Arg72Pro single nucleotide polymorphisms and the susceptibility to gliomas in individuals from Southeast Brazil. Genet. Mol. Res., 7: 207-216.

Pollett, A., Y.C. Bedard, S.Q. Li, T. Rohan and R. Kandel, 2000. Correlation of p53 mutations in ThinPrep-processed fine needle breast aspirates with surgically rese-cted breast cancers. Mod. Patholol., 13: 1173-1179.

Portwine, C., S. Chilton-MacNeill, C. Brown, E. Sexsmith, J. McLaughlin and D. Malkin, 2001. Absence of germline and somatic p53 alterations in children with sporadic brain tumors. J. Neuro Oncol., 52: 227-235.

Raja, A.S.M. and G. Thilagavathi, 2011. Influence of enzyme and mordant treatments on the antimicrobial efficacy of natural dyes on wool materials. Asian J. Textile, 1: 138-144.

Rocco, F., 2011. Technical textile based on regenerated wool: Process and test of a new generation of fabrics. Asian J. Textile, 1: 42-49.

Sameer, A.S., Z.A. Shah, N. Syeed, M.Z. Banday, S.M. Bashir, B.A. Bhat and M.A. Siddiqi, 2010. TP53 Pro47Ser and Arg72Pro polymorphisms and colorectal cancer predisposition in an ethnic Kashmiri population. Genet. Mol. Res., 9: 651-660.

Sanchez-Prieto, R., J.M. Rojas, Y. Taya and J.S. Gutkind, 2000. A role for the p38 mitogen-acitvated protein kinase pathway in the transcriptional activation of p53 on genotoxic stress by chemotherapeutic agents. Cancer Res., 60: 2464-2472.

Santos, L.E.M.C., A.C.T. Guilhen, R.A. Andrade, L.G. Sumi and L.S. Ward, 2011. The role of TP_{53} Pro_{47}Ser and Arg_{72}Pro single nucleotide polymorphisms in the susceptibility to bladder cancer. Urol. Oncol., 29: 291-294.

Siraj, A.K., M. Al-Rasheed, M. Ibrahim, K. Siddiqui and F. Al-Dayel *et al.*, 2008. RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. J. Endocrinol. Invest., 31: 893-899.

Takekawa, M., M. Adachi, A. Nakahata, I. Nakayama and F. Itoh *et al.*, 2000. p53-inducible wip1 phosphatase mediates a negative feedback regulation of p38MAPK-p53signaling in response to UV radiation. EMBO J., 19: 6517-6526.

Taubert, H., B. Thamm, A. Meye, F. Bartel and A.K. Rost *et al.*, 2008. The p53 status in juvenile chronic arthritis and rheumatoid arthritis. Clin. Exp. Immunol., 122: 264-269.

Walters, J.J., W. Muhammad, K.F. Fox, A. Fox, D. Xie, K.E. Creek and L. Pirisi, 2001. Genotyping single nucleotide polymorphisms using intact polymerase chain reaction products by electrospray quadrupole mass spectrometry. Rapid Commun. Mass Spectrom., 15: 1752-1779.

Whibley, C., P.D. Pharoah and M. Hollstein, 2009. P53 polymorphisms: Cancer implications. Nat. Rev. Cancer, 9: 95-107.

Yang, Y., Z. Xiao, W. Chen, H. Sang and Y. Guan *et al.*, 2004. Tumor suppressor gene *TP53* is genetically associated with schizophrenia in the Chinese population. Neurosci. Lett., 369: 126-131.