Genetic Syndromes & Gene Therapy

Dholariya et al., J Genet Syndr Gene Ther 2013, 4:5
http://dx.doi.org/10.4172/2157-7412.1000145

Research Article Open Access

TP53 Gene Polymorphism in Epithelial Ovarian Carcinoma Patients from North Indian Population and its Pro/Pro Variant is Potentially Contributing to Cancer Susceptibility

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Abstract

Background: Ovarian cancer is the leading cause of death from gynecological malignancies. The early stages of this disease are asymptomatic and more than 75% of the cases are diagnosed with regional or distant metastases. **P53** is a tumor suppressor gene and is involved in the etiology of ovarian cancer. Studies investigating the associations between the *p53* codon 72 polymorphism and ovarian cancer risk showed conflicting results. A polymorphism at codon 72 of the human tumour-suppressor gene, p53, results in translation to either arginine or proline. To investigate the association of p53 codon 72 polymorphism with susceptibility to epithelial ovarian cancer in North Indian women and to correlate them with clinicopathological characteristics of disease.

Methods: The study was conducted on 100 epithelial ovarian cancer patients and 100 healthy controls. Genotyping of p53 codon 72 polymorphism was examined by PCR with allele-specific primers.

Results: The proportions of individuals homozygous for the arginine allele, homozygous for the proline allele, and heterozygous for the two alleles were 33%, 17%, and 50% among women screened for ovarian cancer; 62%, 6%, and 32% among the control group. A significant correlation was found between the arg/pro ($p<0.0004$) and pro/pro ($p<0.0006$) genotypes with respect to the arg/arg genotype. Pro/pro genotype emerged as the risk factor with an OR of 5.3 and a RR of 2.5.

Conclusion: Our study suggests that Pro/Pro genotype of 72 codon polymorphism could be an independent susceptibility marker in northern Indian women with ovarian carcinomas.

Keywords: Epithelial ovarian cancer; ASO-PCR; Arg72Pro; TP53 polymorphism

Abbreviations: EOC: Epithelial Ovarian Cancer; ASO-PCR: Allele Specific Oligonucleotide-Polymerase Chain Reaction; OR: Odd Ratio; RR: Risk Ratio

Introduction

Ovarian cancer is the sixth most common cancer worldwide [1]. In India, ovarian cancer is the third leading site of cancer among women, after cervix and breast cancer. Epithelial ovarian cancer is the most lethal of all gynaecological malignancies accounting for 52% of all gynaecological cancer related deaths [2] in early stage maximum patients are asymptomatic, and more than 75% cases are diagnosed at late stage. Patients with advance disease have poor prognosis with 5 year survival rate of only 10-20% despite best possible treatment [3]. Ovarian cancer continues to be the most lethal of the gynaecologic malignancies due to the lack of early detection, screening strategies and ineffective therapeutics for late-stage metastatic disease, particularly in the recurrent setting [4].

Genetic variations such as functional polymorphisms may be associated with the development of ovarian cancer as ovarian cancer is a multistep disease. In humans, p53 (protein 53 or tumor protein 53), is a tumor suppressor protein that is encoded by the *TP53* gene. It plays a key role in stress responses like DNA damage, hypoxia, metabolic stress and oncogene activation and maintains genomic integrity. p53 exercises its protective roles as a transcription factor. By binding to specific response elements in DNA, p53 modulates the transcription of genes that govern the major defenses against tumor growth, which include cell cycle arrest, apoptosis, inhibition of angiogenesis and cellular senescence. p53 also interacts with numerous cellular proteins, including several that control programmed cell death, and these molecular interactions might contribute to the inhibitory role of p53 in tumorigenesis [5].

Malfunction of the p53 activity is an almost universal hallmark of human tumors. Mutant proteins are defective in DNA binding in a sequence-specific manner, and thus in the up regulation of downstream genes [6]. So far 13 polymorphisms have been described in this gene [7]. 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 (CGC) by proline (CCC) in the transactivating domain. These two polymorphic variants (Pro72 and Arg72) alter the structure and function of the *p53* protein [8]. The potential consequence of this amino acid exchange is differences in the susceptibility to malignant transformation, induction of apoptosis, and transcriptional activity [9]. The arginine (Arg72) allele increases

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Received May 02, 2013; **Accepted** June 07, 2013; **Published** June 10, 2013

Citation: Dholariya S, Zubari M, Ray PC, Gandhi G, Khurana N, et al. (2013) TP53 Gene Polymorphism in Epithelial Ovarian Carcinoma Patients from North Indian Population and its Pro/Pro Variant is Potentially Contributing to Cancer Susceptibility. J Genet Syndr Gene Ther 4: 145. doi:10.4172/2157-7412.1000145

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 phase of the cell cycle [10].

Many molecular epidemiologic data found that these polymorphisms are likely candidate genetic markers of certain cancers. In fact, there are discrepancies about the distribution of p53 codon 72 polymorphism in different malignancy. As a tumor suppressor gene p53 72 codon polymorphism might impact individual susceptibility to carcinogenesis. Based on this hypothesis, we carried out a hospital-based case-control study [pilot study] to determine the frequency of TP53 (rs1042522, G>C) 72 codon polymorphic variants among epithelial ovarian cancer and to investigate its association with clinicopathological features.

Materials and Methods

Study population

The study was conducted in Cancer Genetics Lab, Department of Biochemistry, Maulana Azad Medical College in collaboration with department of Obstetrics and Gynaecology, Lok Nayak Hospital, New Delhi. It was a hospital based case-control study. A total of 100 epithelial ovarian cancer (EOC) patients and 100 age-matched healthy females were included in the study. EOC patients were assessed on the basis of clinical and pathological parameters. Diagnosis of all tumors was verified by two senior pathologists. The cancer was staged in according to the International Federation of Gynaecology and Obstetrics surgical staging system (FIGO). Informed consent form signed by all patients and research protocol was approved by the Local ethical committee.

Sample collection and DNA extraction

Blood samples from newly diagnosed 100 EOC patients and 100 non-cancer individuals as controls were selected from an ongoing molecular study of EOC in the Cancer Genetics Lab, Department of biochemistry, MAMC. Patients with a history of previous cancer or metastasized cancer from other organs except Ovary were excluded. All controls, like the cases, were the residents of north India. Written informed consent was obtained from all participants and patient follow up was obtained through hospital records as well as by direct patient contact. The study was approved by the institutional ethics committee, MAMC, New Delhi. Blood samples were collected in an anti-coagulated with EDTA tubes were stored at -70°C until use and genomic DNA was extracted using DNA sure blood mini kit (Nucleo-pore Genetix brand).

Genotyping of p53 codon 72 polymorphism

TP53 (Arg72Pro) polymorphism in promoter was identified by ASO-PCR. Each reaction was performed in a total volume of 25 µl containing 12.5 µl Master Mix (Fermentas), a working concentration of 25pm for each primer as shown in Table 1 and 0.1- 0.2 µg template DNA.

PCR Amplif cation

The initial denaturaion at 94°C for 10 minutes, followed by 40 cycles of final denaturation at 94°C for 45 seconds, annealing at 55°C for 45 seconds (for arginine), 60°C for 45 seconds (for proline), extension step at 72°C for 45 seconds and final extension step at 72°C for 10 minutes. PCR results were analysed without knowledge of the subjects' case-control status. Fifteen samples were randomly selected for repeated assay to know the specificity of results and the results were 100% agreeable. The PCR products were visualized with ethidium bromide on a 2% agarose gel under UV-transillumination. The products obtained had a band-size of 141 bp and 177 bp for arginine and proline respectively as depicted in Figures 1a-1c.

UV Transillumination

Statistical analysis

All statistical analysis was performed using SPSS software version 17.0. Chi-square test was used to examine the differences in frequency distribution of demographic variables, staging, grading, allele and genotype distribution between cases and controls. Association between the gene polymorphism and occurrence of cancer was estimated by Odd ratio and Risk Ratio and their 95% CIs. p-value <0.05 was considered statistically significant.

Results

Study population

The baseline characteristics of subjects are summarized in Table 2. The subjects (EOC) were divided into two groups, ≤ 40 years (32%) and >40 years (68%).

To know the effect of p53 polymorphism on clinicopathological features, cases were divided according to the FIGO staging of EOC, histopathological types and histopathological grade. In this study, highest number of cases was in stage III (70%) as compared to stage IV (11%), stage II (10%) and stage I (9%). According to histopathological types highest number of cases was in mucinous (45%) and serous adenocarcinoma (45%), mixed adenocarcinoma (5%), endometroid adenocarcinoma (3%) and clear cell adenocarcinoma (2%). In histopathological grade highest number of cases was in moderately differentiated (66%) as compared to poorly differentiated (20%) and well differentiated (14%). No patients had a family history of epithelial ovarian cancer.

Allele and genotype distribution

Allele and genotype distribution are described in Table 4. The allele frequencies of TP53 Arg and TP53 Pro were 0.58 and 0.42 in cases, and 0.78 and 0.22 in controls respectively. TP53 different genotypes were compared with cases and controls. There were significant difference of genotypes between cases and controls (p=0.0001). The result shows that Arg/Arg allele is more frequent (0.78) in controls as against those in cases (0.58). On the other hand, Pro/Pro allele was more incessant in cases (0.42) as compared to controls (0.22), represented graphically in Figure 2.

It showed that patients who expressed TP53 Pro allele had a significantly increased risk of developing EOC compared with those

	Primer sequence of p53 R72P G>C (rs1042522)	Product size	Annealing Tempt
Arg72 allele	F -5'-TCCCCCTTCCCGTCCCAA-3'	141 bp	55°C
	R- 5'-CTGCTGCAGGGGCCACGC-3'		
Pro72allele	F-5'-GTCCTCTGACTGCTGTTATCACCCATCTAC-3'	177 bp	60°C
	R-5'- GGGATACGGCCAGGCATTGAAGTCTC-3'		

Table 1: Primer sequence for ASO-PCR used for p53 codon 72 polymorphism.

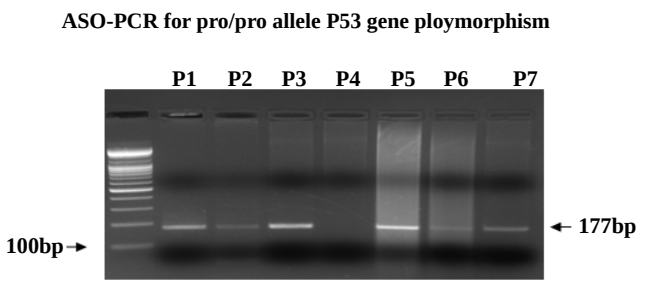

Figure 1a: Gel electrophoresis band pattern of Pro allele as visualized on a 2% agarose gel under UV transillumination.

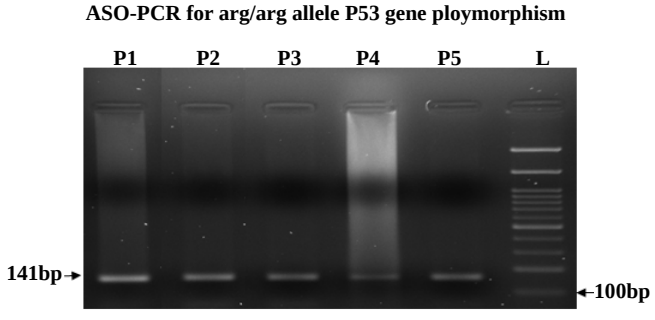

Figure 1b: Gel electrophoresis band pattern of arg allele as visualized on a 2% agarose gel under UV transillumination.

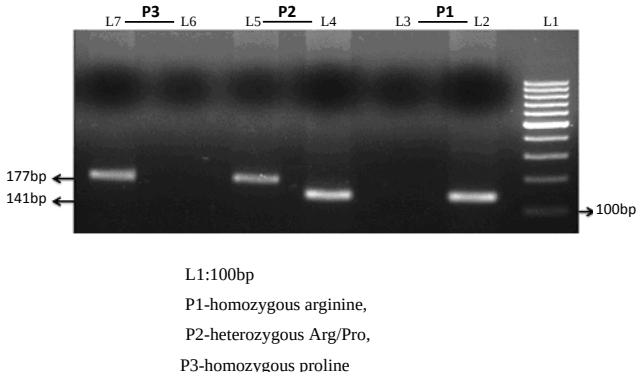

Figure 1c: Gel electrophoresis band pattern of arginine and proline allele as visualized on a 2% agarose gel under UV transillumination.

who expressed TP53 Arg allele (p=0.0001). The evaluation by OR and RR with 95% CI each predicted that Pro/Pro is a high risk factor for EOC patients with an OR of 5.3 (1.9-14.7) and RR of 2.5 (1.2-5.0) as depicted in Table 3.

P53 codon 72 polymorphism and its association with age at diagnosis

Table 4 describes the association of p53 codon 72 polymorphism and its association with age at diagnosis. In both groups ≤ 40 years and >40 years, Arg/Pro genotypes was found to be more prevalent (53.1% and 48.5% respectively). There was however, no significant correlation between the p53 polymorphism and age.

P53 codon 72 polymorphism and its association with stage

The frequency and distribution of alleles analysed in the women with ovarian cancer with respect to early and advanced stages, homozygous for the arginine allele, homozygous for the proline allele, and heterozygous for the two alleles were 32%, 26%, and 40% and in advanced stage the homozygous for the arginine allele, homozygous for

Variables	Cases n (%)	Controls n (%)
AGE		
<40 years	32(32)	56(56)
≥40 years	68(68)	44(44)
STAGING		
I	9(9)	
II	10(10)	
III	70(70)	
IV	11(11)	
HISTOPATHOLOGY		
Mucinous	45(45)	
Serous	45(45)	
Endometroid	3(3)	
Clear Cell	2(2)	
Mixed	5(5)	
GRADING		
Well differentiated	14(14)	
Moderately differentiated	66(66)	
Poorly differentiated	20(20)	

Table 2: Baseline characteristics of subjects involved in the study.

Genotype	Cases n(%)	Controls n(%)	OR (95% CI)	RR (95% CI)	p-value
Arg/Arg	33(33)	62(62)	1(ref)	1	
Arg/Pro	50(50)	32(32)	2.9 (1.5-5.4)	1.6(1.2-2.2)	0.0004
Pro/Pro	17(17)	06(6)	5.3(1.9-14.7)	2.5(1.2-5.0)	0.0006

Table 3: Odd Ratio of p53 codon 72 Polymorphism in Cases and Controls.

Parameters	Arg/Arg n (%)	Arg/Pro n (%)	Pro/Pro n (%)	Arg allele	Pro allele	Chi Sq.	df	p-value
Cases(100)	33(33)	50(50)	17(17)	0.58	0.42	18.06	2	0.0001
Contros(100)	62(62)	32(32)	06(6)	0.78	0.22			
Age								
≤40 years	8(25)	17(53.1)	7(21.8)	0.52	0.48	1.66	2	0.43
> 40 years	25(36.7)	33(48.5)	10(14.7)	0.61	0.39			
Stage								
I	3(33.3)	4(44.4)	2(22.2)	0.56	0.44	9.5	6	0.14
II	3(30.0)	4(40.0)	3(30.0)	0.5	0.5			
III	26(37.1)	32(45.7)	12(17.1)	0.6	0.4			
IV	1(9.09)	10(90.9)	--	0.55	0.45			
Histopathology								
Mucinous	16(35.5)	21(46.6)	8(17.7)	0.59	0.41	5.89	8	0.65
Serous	15(33.3)	25(55.5)	5(11.1)	0.61	0.39			
Endometroid	1(33.3)	1(33.3)	1(33.3)	0.5	0.5			
Clear Cell	--	1(50)	1(50)	0.25	0.75			
Mixed	1(20.0)	2(40.0)	2(40.0)	0.4	0.6			
Grade								
Well differentiated	5(35.7)	8(57.1)	1(7.1)	0.64	0.36	3.4	4	0.47
Moderately differentiated	19(28.7)	36(54.5)	11(16.6)	0.56	0.44			
Poorly differentiated	8(40.0)	7(35.0)	5(25.0)	0.57	0.43			

Table 4: Association of p53 gene polymorphism in EOC patients with their clinicopathological features.

the proline allele, and heterozygous for the two alleles was 33%, 52%, and 15%. No significant correlation was found between the arg/pro and pro/pro genotypes with respect to the arg/arg genotype. There was no association between p53 codon 72 polymorphism and FIGO staging although the Arg/Pro genotype was consistently higher in early as well as in advanced stages as shown in Table 5b.

P53 codon 72 polymorphism and its association with histopathology

The Pro/Pro allele was distinguished to be higher (0.75) than the Arg/Arg allele (0.25) in clear cell adenocarcinoma, but no significant association was found between the p53 polymorphism and other adenocarcinoma.

P53 codon 72 polymorphism and its association with histopathological grade

No significant correlation was found between the p53 polymorphism and histopathological grade though the Arg/Pro genotype was observed to be predominant in well differentiated (57.1%) and moderately differentiated (54.5%) adenocarcinomas.

Discussion

Most genetics aberrations in tumor suppressor genes and proto-oncogenes are associated with ovarian cancer along with other cancers. As p53 is an important tumor suppressor gene, p53 gene mutation were frequently observed in ovarian cancer [11]. Detection of p53 mutation is helpful for early diagnosis and prognosis of cancer. Recently, studies on p53 codon 72 polymorphism revealed that this polymorphism may be associated with many tumours like breast cancer [12], hepatocellular carcinoma [13], oral squamous cell carcinoma [14], leukemia [15], oesophageal and lung cancer [16]. In p53 gene, codon 72 polymorphism is the most common polymorphic site. Several studies described the association between this polymorphism and ovarian cancer, but the results were conflicting because of different genotyping methods, selection bias and ethinicity influences. In the present study, genotype Arg/Pro was found to be more frequent than in controls. Arg allele was observed to be more persistent in the healthy controls. Pro allele is more susceptible to develop ovarian carcinoma as compared to Arg allele. Individual parity was observed with respect to the Pro/Pro genotype in Chinese [17], Canadian [18], Indian [19], Thai [20], Brazilian [21], Taiwanese [22] and Portugese [23] populations as shown in Table 5a.

When the frequency distribution of pro/pro genotype was analyzed between cases and controls, an idiosyncratic determination was observed in different cancers such as lung cancer [24,25], colorectal cancer [26], thyroid cancer [27], nasopharyngeal cancer [28] and oral squamous cell carcinoma [29] with the present study as depicted in Table 6. A significant association was seen in all cancers with a $p<0.05$.

Codon 72 situated at hydrophobic region of the protein that decide its conformation, transcriptional and DNA binding activity which necessary for growth suppression. In TP53 gene, this common polymorphism site located in proline rich domain at 72 codon in exon 4. This is proline is a part of PXXP motif which is extremely important for maintaining structure of SH3 domain containing protein. TP53 protein contains either arginine or proline with different functional activity. Arg variant is more powerful to induce apoptosis than Pro variant because it has variant tendency to localize this protein in mitochondria. In addition to forming a complex with GRP75, mitochondrial p53 also can be found in a complex with Hsp60 which has been shown to co-localize with other pro-apoptotic proteins, including caspase-3, apoptosis-inducing factor (AIF) and Nip, in the mitochondria [30]. While Pro variant is more effective in inducing G1 arrest than Arg variant, due to altered binding affinity of p53 [31] therefore Arg variant could not be a risk allele for ovarian carcinoma. Pro allele also associated with increased susceptibility to nasopharyngeal carcinoma [32], Gastric cancer [33], lung cancer [34] and breast cancer [35]. From these studies showed that p53 codon 72 polymorphism may serve as risk factor for different cancer and this conflict due to different peculiarities of

Region	Cancer Type	Cases n(%)	Controls n(%)	Odd Ratio (95% CI) Pro/Pro vs. Arg/Arg	Author
China	Nasopharyngeal Carcinoma	64	99	2.00 (0.86-4.67)	Golovleva et al. [17]
Canada	Head & Neck Cancer	163	163	1.08 (0.36-3.20)	Hamel et al. [18]
India	Oral Squamous Cell Carcinoma	110	26	4.40 (0.90-21.56)	Nagpal et al. [19]
Thailand	Nasopharyngeal Cancer	102	148	1.93 (0.94-3.98)	Tiwawech et al. [20]
Brazil	Head & Neck Cancer	50	142	3.27 (0.90-11.87)	Cortezzi et al. [21]
Taiwan	Hypopharyngeal Carcinoma	53	53	3.67 (1.16-11.56)	Twu et al. [22]
Portugal	Nasopharyngeal Carcinoma	107	285	2.62 (1.10-6.30)	Sousa et al. [23]
Present Study	Epithelial Ovarian Cancer	100	100	5.3 (1.9-14.7)	2013

Table 5a: Association of p53 codon 72 polymorphism between cases & controls & the risk of developing various cancers.

Staging		Arg/Arg (%)	Arg/Pro (%)	Pro/Pro(%)
Early stage I/II	**19**	6(32%)	8(40%)	5(26%)
Advanced disease	**81**	27(33%)	42(52%)	12(15%)

Table 5b: Frequency and distribution of P53 codon 72 polymorphism alleles with respect to stage.

Region	Cancer Type	Pro/Pro Genotype		p-Value	Author
		(Cases) n(%)	(Controls) n(%)		
Taiwan	Lung Cancer	15(41.7)	8(20.0)	0.01	Wang et al. [24]
USA	Lung Cancer	79(16.4)	61(12.0)	0.03	Fan et al. [16]
China	Colorectal Cancer	85(24.6)	105(15.7)	<0.0001	Zhu et al. [26]
Turkey	Thyroid Cancer	13(22.4)	10(8.7)	<0.05	Aral et al. [27]
Tunisia	Nasopharyngeal Cancer	23(20.0)	6(7.0)	0.03	Hadhri et al. [28]
India	Oral Squamous Cell Carcinoma	22(14.6)	7(4.6)	0.005	Addala et al. [29]

Table 6: Frequency Distribution of Pro/Pro Genotype-TP53 codon 72 polymorphism between cases & controls & its association with different cancers.

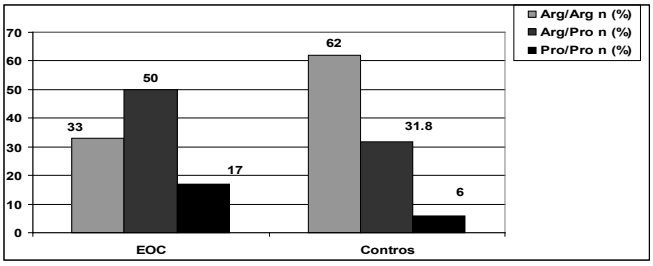

Figure 2: TP53 (Arg72Pro) polymorphism and its allele frequencies among EOC vs. Controls.

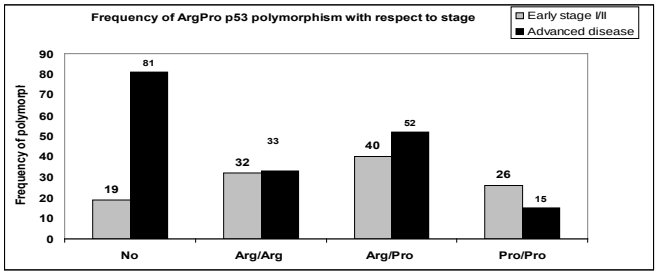

Figure 3: P53 codon 72 polymorphism and its association with histopathology: The Pro/Pro allele was distinguished to be higher (0.75) than the Arg/Arg allele (0.25) in clear cell adenocarcinoma, but no significant association was found between the p53 polymorphism and other adenocarcinoma.

tumor, sample size and ethnic variation in di□erent geographical area. Our results suggest that Pro/Pro genotype is strongly associated with ovarian cancer progression in North Indian population. □e variation in the p53 codon 72 allelotype is an example of an intermediate risk polymorphism which may play a role in ovarian carcinogenesis and di□erentially in□uence cellular DNA repair and apoptotic pathways. □ese □ndings may have a proli□c outcome for gene-targeted therapies in the treatment of epithelial ovarian cancer.

Conclusion

In summary, our data suggest that there was signi□cant association between p53 codon 72 polymorphism and occurrence of epithelial ovarian cancer. p53 Pro72 may be a potential genetic predisposing factor for epithelial ovarian cancer development in north Indian women. Study on larger sample size should be performed to understand the role of p53 codon 72 polymorphism in ovarian cancer.

Acknowledgements

We gratefully acknowledge the assistance of UGC for providing us with the grant and Maulana Azad Medical College and Lok Nayak Hospital, New Delhi for assistance in recruiting the subjects.

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Citation: Dholariya S, Zubari M, Ray PC, Gandhi G, Khurana N, et al. (2013) TP53 Gene Polymorphism in Epithelial Ovarian Carcinoma Patients from North Indian Population and its Pro/Pro Variant is Potentially Contributing to Cancer Susceptibility. J Genet Syndr Gene Ther 4: 145. doi:10.4172/2157-7412.1000145

This article was originally published in a special issue, **Cancer Genetics** handled by Editor(s). Dr. Ahmed M Malki, Alexandria University, Egypt