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RESEARCH ARTICLE

Linkage disequilibrium and haplotypes of five *TP53* polymorphisms in oesophageal cancer patients

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Abstract. The aim of present study was to evaluate the linkage disequilibrium (LD) of p.R72P, PIN3 Ins16bp, p.P47S, p.R213R and r.13494g>a polymorphism of *TP53* and their haplotypes association with oesophageal cancer risk in patients from Punjab, northwest India. A total of 466 samples, including 233 oesophageal cancer patients and 233 healthy individuals were analysed. Data analysis revealed the gender specific association. In female group, arginine–proline (RP) genotype ($P = 0.08$) and P allele ($P = 0.07$) of p.R72P polymorphism was marginally associated with increased risk of oesophageal cancer. A1A2 genotype ($P = 0.06$) and A2 allele ($P = 0.07$) of PIN3 Ins16bp polymorphism was marginally associated with decreased risk of oesophageal cancer in male group. A1A2–GA genotype combination ($P = 0.04$) of PIN3 and r.13494g>a polymorphisms was significantly associated with decreased risk of oesophageal cancer in male group. In female group, PP–GA genotype combination ($P = 0.02$) of p.R72P and r.13494g>a polymorphisms and RP–A1A1–GG genotype combination ($P = 0.04$) of p.R72P, PIN3 and r.13494g>a polymorphisms was significantly associated with increased risk of oesophageal cancer. We observed moderate LD between two intronic polymorphisms PIN3 Ins16bp and r.13494g>a ($D' = 0.90$; $r^2 = 0.68$). Haplotype analysis revealed that none of the haplotype combination was associated with oesophageal cancer risk when both the genders were considered. Stratification on the basis of gender showed that P-A2-P-A-A haplotype of p.R72P, PIN3 Ins16bp, p.P47S, p.R213R and r.13494g>a polymorphisms was marginally associated with reduced oesophageal cancer risk in male group ($P = 0.08$). Replication of these findings in independent cohorts may be insightful for the role of *TP53* in oesophageal cancer pathogenesis.

Keywords. oesophageal cancer; *TP53* polymorphism; polymorphism; haplotype; linkage disequilibrium.

Introduction

The susceptibility of individual for the occurrence of common cancers is determined by the genetic variants in genes controlling DNA repair and cell proliferation (Hunt *et al*. 2013). Thus, the genes involved in tumourigenesis are the potential molecular markers associated with susceptibility to cancer. The *TP53* (MIM: 191170), one of the most important tumour suppressor genes, encodes 53-kDa protein which plays a central role in the maintenance of genomic integrity. This tumour suppressor gene is mutated frequently in various solid tumours, which result in the absence or dysfunction of the corresponding protein (Leroy *et al*. 2014). In sporadic human tumours, *TP53* inactivation leads to inactivation of a wide range of anti-proliferative responses which regulate cell cycle progression, apoptosis, autophagy, differentiation, senescence, DNA repair, immune response and oxidative metabolism (Levine 1997; Hainaut and Hollstein 2000; Petitjean *et al*. 2007; Levine and Oren 2009; Suzuki and Matsubara 2011). The *TP53* gene is highly polymorphic and to date more than 500 polymorphisms in both coding and noncoding regions have been identified showing

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geographic and population specific variations (http://p53.iarc.fr). It has been reported that alteration in the amino acid sequence can change the ability of p53 to bind response elements of the target genes, change recognition motifs for post-translational modifications or affect the protein stability (Bergamaschi *et al*. 2003; Li and Prives 2007).

Genetic polymorphisms may contribute for the difference between susceptibility of individuals to various cancers by affecting gene expression regulation (Wade *et al*. 2013). The single-nucleotide polymorphisms (SNPs) play a critical role in individual variation in cancer susceptibility (Whibley *et al*. 2009; Litviakov *et al*. 2010). Genetic association studies have reported SNPs as important tools for targeting the genes responsible for cancer susceptibility (Cao *et al*. 2009). Polymorphisms analysis has revealed the association between specific allele variants and cancer predisposition in a variety of genes (Rogler *et al*. 2011). Polymorphisms affecting the coding sequence of a gene may result in changes that alter protein's function and contribute to genetic instability and error accumulation due to reduced protein activity. Identification of these alterations may help in selecting patients with a higher risk of developing cancer, allowing optimization of treatments (Lacerda *et al*. 2005).

The two functionally important polymorphisms, p.P47S in N-terminal transactivation domain and p.R72P in proline-rich region of p53, play an important role in the apoptosis (Slee *et al*. 2004). It has been documented that the S47 phenotype has a low capacity to induce apoptosis as compared to wild-type P47 phenotype (Li *et al*. 2005; Murphy 2006). Cisplatin and BET inhibitor, OTX-015, showed superior efficacy on S47 tumours as compared to wild-type P47 (Basu *et al*. 2016; Barnoud *et al*. 2018). p.R72P polymorphism located in exon 4 of *TP53* has been extensively studied for its potential association with cancers. Wild-type p53 protein with 72 Arg allele has been reported to be more efficient in inducing apoptosis as compared to 72 Pro allele (Dumont *et al*. 2003). p.R213R (rs 1800372) is an evolutionarily highly conserved rare polymorphism in DNA-binding domain located in exon 6 of *TP53*, which results in alteration of CGA to CGG at codon 213.

Introns are critical components of the eukaryotic genome which play important role in mRNA splicing (Davis *et al.* 2009), gene expression (Goessl *et al.* 1997; Furihata *et al.* 2002; Xinarianos *et al.* 2002) and DNA protein interactions (Smith and Fornace 1996). PIN3 Ins 16bp (rs17878362) located in intron 3 and r.13494g>a located in intron 6 are the most studied intronic polymorphisms of *TP53*. The PIN3 Ins16bp polymorphism has been associated with a lower level of p53 transcript, resulting in altered mRNA processing (Gemignani *et al.* 2004). Recently, r.13494g>a has been reported to be associated with poor prognosis in low rectal cancer (Zhang *et al*. 2019).

A number of studies have investigated the association between p.R72P, PIN3 16bp ins, P.R213R and r.13494g>a polymorphisms and oesophageal cancer (EC) but the results are conflicting as discussed in our previous study (Kaur *et al*. 2014). Haplotype analysis when compared to individual SNP analysis gives more informative results since the cumulative effect of different SNPs in the pathogenesis of the disease. Till date, the LD and role of *TP53* haplotypes have not yet been investigated in EC susceptibility. LD and haplotype analyses are important strategies for identifying the genetic determinants of susceptibility to complex diseases (Trifonova *et al*. 2012). Therefore, the aim of present case–control study was to invetigate the LD of p.R72P, PIN3 Ins 16bp, P.R213R and r.13494g>a polymorphism of *TP53* and the probable association of their haplotypes with EC risk. Awareness of the association between genetic alteration and EC can improve the prognosis and treatment of cancer.

Material and methods

Study groups

The present case–control study was carried out in collaboration with Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, India. In this study, 233 clinically confirmed oesophageal cancer patients (96 males and 137 females) and 233 (96 males and 137 females) unrelated, age and gender matched healthy individuals were analysed. The control subjects were randomly selected from same geographical area as of the patients, i.e. Punjab, northwest India. The age of the patients ranged from 24 to 90 years and of controls ranged from 24 to 87 years. The experimental design of present study was approved by the ethics committee of Guru Nanak Dev University Amritsar, Punjab, India. Written informed consent was obtained from all study participants.

Genotyping and analysis of data

The methods for genotyping of five *TP53* polymorphisms and analysis of data have been described in our previous study (Kaur *et al*. 2014). Pair-wise LD was calculated between five SNPs of *TP53* in patients and controls using SHEsis software (Shi and He 2005). The SHEsis software platform was used to calculate the haplotype frequencies and the frequencies were based on expectation–maximization algorithm (Li *et al*. 2009).

Results

In this case–control study a total of 466 subjects; 233 oesophageal cancer patients and 233 controls were analysed. Mean age of the patients at diagnosis was 55.90 ± 12.86 years while the mean age of the controls was 54.75 ± 12.60 years. The demographic and clinical characteristics of EC patients and healthy controls are provided in tables 1 and 2. About 73.0% of patients developed EC after the age of 50

Table 1. Characteristics of oesophageal cancer patients and controls.

Variables	Patients *n* (%)	Controls *n* (%)
Gender		
Male	96 (41.2)	96 (41.2)
Female	137 (58.8)	137 (58.8)
Age (year)		
< 50	63 (27.0)	74 (31.8)
≥ 50	170 (73.0)	159 (68.2)
Mean ± SD	55.90±12.86	54.75±12.60
Range	24–90	24–87
Habitat		
Rural	188 (80.7)	188 (80.7)
Urban	45 (19.3)	45 (19.3)
Habits		
Diet		
Vegetarian	116 (49.8)	125 (53.6)
Occasionally nonvegetarian	117 (50.2)	108 (46.4)
Alcohol consuming		
Never	155 (66.5)	162 (69.5)
Ever	78 (33.5)	71 (30.5)
Males	75 (32.2)	71 (30.5)
Females	3 (1.3)	–
Smoking status		
Never	196 (84.1)	214 (91.8)
Ever	37 (15.9)	19 (8.2)
Males	33 (14.2)	13 (5.6)
Females	4 (1.7)	6 (2.6)
Alcoholic + smoking	32 (13.7)	11 (4.7)
Males	30 (12.9)	11 (4.7)
Females	2 (0.9)	–
Occupation		
Farmers	78 (33.5)	74 (31.8)
Housewives	116 (49.8)	102 (43.8)
Others*	39 (16.7)	57 (24.4)
Menstrual status		
Premenopausal	34 (24.8)	39 (28.5)
Postmenopausal	103 (75.2)	98 (71.5)

*Business, employee etc.

Table 2. Clinical characteristics of oesophageal cancer patients.

Parameter	Total *n* (%)	Males *n* (%)	Females *n* (%)
Stage of Cancer			
I	27 (11.6)	15 (15.6)	12 (8.8)
II	94 (40.3)	36 (37.5)	58 (42.3)
III	59 (25.3)	22 (22.9)	37 (27.0)
IV	31 (13.3)	9 (9.4)	22 (16.1)
Unknown	22 (9.4)	14 (14.6)	8 (5.8)
Pathological type			
Squamous cell carcinoma	217 (93.1)	85 (88.5)	132 (96.4)
Adenocarcinoma	16 (6.9)	11 (11.5)	5 (3.6)
Location			
Upper	56 (24.0)	18 (18.7)	38 (27.7)
Middle	67 (28.8)	23 (24.0)	44 (32.1)
Lower	98 (42.1)	45 (46.9)	53 (38.7)
Indeterminate	12 (5.1)	10 (10.4)	2 (1.5)

years. The number of female patients (n = 137) was higher compared to male patients (n = 96).

Risk estimation for TP53 genotypes and haplotypes

The distribution of genotypes in three *TP53* polymorphisms in controls was in agreement with Hardy–Weinberg equilibrium (table 1 in electronic supplementary material at http://www.ac.in/jgenet/). All the patients and controls had wild-type genotype for p.P47S and p.R213R polymorphisms (monomorphic). There was no significant difference in genotype, allele frequencies (table 1 in electronic supplementary material) and genetic models (table 2 in electronic supplementary material) of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphism of *TP53* in total EC patients and controls ($P > 0.05$). When the data of *TP53* polymorphisms was stratified by gender, the association was gender specific (table 3). In female group, arginine–proline (RP) genotype and P allele of p.R72P polymorphism was marginally associated with increased risk to EC. On the other hand, A1A2 genotype ($P = 0.06$), A2 allele ($P = 0.07$) and dominant model ($P = 0.05$) of PIN3 Ins16bp polymorphism was marginally associated with decreased risk to EC in male group. Genetic model analysis showed a statistically significant association between p.R72P polymorphism and EC risk in dominant model ($P = 0.04$) in females (table 4).

After the genotype and allele frequency analyses, the interaction analysis between p.R72P, PIN3 and r.13494g>a polymorphisms was performed. All the possible genotype combinations were evaluated for p.R72P and PIN3, p.R72P and r.13494g>a, PIN3 and r.13494g>a and p.R72P, PIN3 and r.13494g>a polymorphisms (table 3 in electronic supplementary material). Stratification of the subjects on the basis of gender revealed that A1A2–GA genotype combination of PIN3 and r.13494g>a polymorphisms was significantly associated with decreased risk of oesophageal cancer in male group ($P = 0.04$). In female group, PP–GA genotype combination of p.R72P and r.13494g>a polymorphisms ($P = 0.02$) and RP–A1A1–GG genotype combination of p.R72P, PIN3 and r.13494g>a polymorphisms ($P = 0.04$) was significantly associated with increased risk of EC (table 5).

The LD between the *TP53* polymorphisms (p.R72P, PIN3 Ins16bp, p.P47S, p.R213R and r.13494g>a) was calculated based on the Lewontin's standardized disequilibrium coefficient (D') and correlation coefficient (r^2). We observed moderate LD between PIN3 Ins16bp and r.13494g>a intronic polymorphisms of *TP53* ($D' = 0.90$; $r^2 = 0.68$) in total subjects (figure 1, a&b) and also in both male ($D' = 0.97$; $r^2 = 0.69$) (figure 1, c&d) and female ($D' = 0.86$; $r^2 = 0.68$) groups (figure 1, e&f).

Distribution of haplotypes of five (p.R72P, PIN3 Ins16bp, p.P47S, p.R213R and r.13494g>a) polymorphisms of *TP53* were further analysed to evaluate their combined effect. Haplotype R-A1-P-A-G was the most common in both oesophageal cancer patients and controls. The frequency of P-A1-P-A-A haplotype was higher (37%) in female group. In total samples, no particular haplotype combination showed association with EC risk. When analysis was done on the basis of gender, it was observed that P-A2-P-A-A haplotype was marginally associated ($P = 0.08$) with reduced EC risk in male group (table 6).

Discussion

SNPs in genes involved in tumourigenesis have been reported to play important roles in cancer development. Several studies have investigated the association of *TP53* variants with cancer risk and the results still remain controversial. The differences in results could be due to the ethnic variations and interactions with genetic and environmental factors involved in the pathogenesis of different cancers. Despite the recent advances in surgical approaches and therapeutics, EC is the eighth most common cause of cancer in the world. In the present case–control study, we analysed the LD of five functional *TP53* polymorphisms as well as the probable association of their haplotypes with oesophageal cancer risk in northwest Indians.

In the present study, we observed moderate LD between PIN3 Ins16bp and r.13494g>a intronic polymorphisms of *TP53* ($D' = 0.90$; $r^2 = 0.68$) in oesophageal cancer patients from Punjab. To the best our knowledge, there is no published study showing LD between *TP53* polymorphisms in EC. Inhabitants of Punjab in northwestern part of India have a mixed ethnic origin with contributions of Caucasian and Indo-Scythian racial elements. LD between some of *TP53* polymorphisms have been reported earlier in patients of Caucasian origin. Strong LD between PIN3 Ins16bp and r.13494g>a polymorphisms has been reported in ovarian (Wang-Gohrke *et al*. 1999) and lung cancer patients (Wu *et al*. 2002). Moderate LD between PIN3 Ins16bp and r.13494g>a, and between PIN3 Ins16bp and p.R72P has been observed in diffuse large B-cell lymphoma patients from Russia (Voropaeva *et al*. 2014).

LD was also observed between r.13494g>a and p.R72P polymorphisms in Romanian colorectal cancer (Murarasu *et al*. 2018) and Norwegian and Polish breast cancer (Garcia-Closas *et al*. 2007) and Russian diffuse large B-cell lymphoma (Voropaeva *et al*. 2014) patients. In the present study, no LD was observed between r.13494g>a and p.R72P polymorphisms.

Table 3. Association of *TP53* polymorphisms with oesophageal cancer risk in males and female patients.

	Male (n = 96)				Female (n = 137)			
Variant	Patient n (%)	Control n (%)	OR (95%CI)	P value	Patient n (%)	Control n (%)	OR (95%CI)	P value
p.R72P (rs1042522)								
Genotype								
RR	21 (21.9)	20 (20.8)	Reference		26 (19.0)	40 (29.2)	Reference	
RP	53 (55.2)	46 (47.9)	1.10 (0.53–2.27)	0.80	73 (53.3)	66 (48.2)	1.70 (0.94–3.09)	0.08
PP	22 (22.9)	30 (31.2)	0.70 (0.31–1.59)	0.19	38 (27.7)	31 (22.6)	1.89 (0.95–3.74)	0.73
Allele								
R	95 (49.5)	86 (44.8)	Reference		125 (45.6)	146 (53.3)	Reference	
P	97 (50.5)	106 (55.2)	0.83 (0.55–1.24)	0.36	149 (54.4)	128 (46.7)	1.36 (0.97–1.90)	0.07
PIN3 Ins16bp (rs17878362)								
Genotype								
A1A1	74 (77.1)	62 (64.6)	Reference		90 (65.7)	91 (66.4)	Reference	
A1A2	19 (19.8)	30 (31.2)	0.53 (0.27–1.03)	0.06	41 (29.9)	41 (30.0)	1.01 (0.60–1.70)	0.97
A2A2	3 (3.1)	4 (4.2)	0.63 (0.14–2.92)	0.84	6 (4.4)	5 (3.6)	1.21 (0.36–4.12)	0.77
Allele								
A1	167 (87.0)	154 (80.2)	Reference		221 (80.7)	223 (81.4)	Reference	
A2	25 (13.0)	38 (19.8)	0.61 (0.35–1.05)	0.07	53 (19.3)	51 (18.6)	0.95 (0.62–1.46)	0.83
r.13494g>a (rs1625895)								
Genotype								
GG	64 (66.7)	55 (57.3)	Reference		82 (59.9)	90 (65.7)	Reference	
GA	27 (28.1)	37 (38.5)	0.63 (0.34–1.16)	0.13	51 (37.2)	42 (30.7)	1.33 (0.8–2.21)	0.27
AA	5 (5.2)	4 (4.2)	1.07 (0.27–4.20)	0.45	4 (2.9)	5 (3.6)	0.88 (0.23–3.38)	0.55
Allele								
G	155 (80.7)	147 (76.6)	Reference		215 (78.5)	222 (81.0)	Reference	
A	37 (19.3)	45 (23.4)	0.78 (0.48–1.27)	0.32	59 (21.5)	52 (19.0)	1.17 (0.77–1.78)	0.46

OR, odds ratio; CI, confidence interval.

Table 4. Genetic models of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphisms and oesophageal cancer risk in males and female patients.

		Male (n = 96)				Female (n = 137)			
Variant	Genetic models	Patient	Control	OR (95%CI)	P value	Patient	Control	OR (95%CI)	P value
p.R72P	Dominant model (RP+PP vs RR)								
	RP+PP	75 (78.1)	76 (79.2)	0.94 (0.47–1.87)	0.86	111 (81.0)	97 (70.8)	1.76 (1.00–3.09)	0.04
	RR	21 (21.9)	20 (20.8)			26 (19.0)	40 (29.2)		
	Codominant model (PP vs RP/RP vs RR)								
	PP	22 (22.9)	30 (31.2)	0.82 (0.55–1.24)	0.35	38 (27.7)	31 (22.6)	1.37 (0.97–1.93)	0.07
	RP	53 (55.2)	46 (47.9)			73 (53.3)	66 (48.2)		
	RR	21 (21.9)	20 (20.8)			26 (19.0)	40 (29.2)		
	Recessive model (PP vs RR+RP)								
	PP	22 (22.9)	30 (31.2)	0.65 (0.34–1.24)	0.19	38 (27.7)	31 (22.6)	1.31 (0.76–2.27)	0.33
	RR+RP	74 (77.1)	66 (68.8)			99 (72.3)	106 (77.4)		
PIN3 Ins16bp	Dominant model (A1A2+A2A2 vs A1A1)								
	A1A2+A2A2	22 (22.9)	34 (35.4)	0.54 (0.29–1.02)	0.05	47 (34.3)	46 (33.6)	1.03 (0.63–1.7)	0.90
	A1A1	74 (77.1)	62 (64.6)			90 (65.7)	91 (66.4)		
	Codominant model (A2A2 vs A1A2/ A1A2 vs A1A1)								
	A2A2	3 (3.1)	4 (4.2)	0.62 (0.36–1.07)	0.08	6 (4.4)	5 (3.6)	1.05 (0.69–1.60)	0.83
	A1A2	19 (19.8)	30 (31.2)			41 (29.9)	41 (30.0)		
	A1A1	74 (77.1)	62 (64.6)			90 (65.7)	91 (66.4)		
	Recessive model (A2A2 vs A1A1+A1A2)								
	A2A2	3 (3.1)	4 (4.2)	0.74 (0.16–3.41)	0.70	6 (4.4)	5 (3.6)	1.21 (0.36–4.06)	0.76
	A1A1+A1A2	93 (96.9)	92 (95.8)			131 (95.6)	132 (96.4)		
r.13494g>a	Dominant model (GA+AA vs GG)								
	GA+AA	32 (33.3)	41 (42.7)	0.67 (0.37–1.21)		55 (40.1)	47 (34.3)	1.28 (0.79–2.10)	0.32
	GG	64 (66.7)	55 (57.3)		0.18	82 (59.9)	90 (65.7)		
	Codominant model (AA vs GA/GA vs GG)								
	AA	5 (5.2)	4 (4.2)	0.78 (0.48–1.27)	0.32	4 (2.9)	5 (3.6)	1.18 (0.77–1.81)	0.45
	GA	27 (28.1)	37 (38.5)			51 (37.2)	42 (30.7)		
	GG	64 (66.7)	55 (57.3)			82 (59.9)	90 (65.7)		
	Recessive model (AA vs GG+GA)								
	AA	5 (5.2)	4 (4.2)	1.26 (0.33–4.86)	0.73	4 (2.9)	5 (3.6)	0.79 (0.21–3.02)	0.73
	GG+GA	91 (94.8)	92 (95.8)			133 (97.1)	132 (96.4)		

OR, odds ratio; CI, confidence interval.

Table 5. Interaction between *TP53* polymorphisms in male and female oesophageal cancer patients.

	Males				Females			
Genotype combination	Patients *n* (%)	Controls *n* (%)	OR (95%CI)	*P* value	Patients *n* (%)	Controls *n* (%)	OR (95%CI)	*P* value
p.R72P-PIN3								
RR-A1A1	21 (21.9)	19 (19.8)	Reference		26 (19.0)	39 (28.5)	Reference	
RR-A1A2	0 (0.0)	1 (1.0)	–		0 (0.0)	2 (1.4)	–	
RP-A1A1	42 (43.7)	30 (31.3)	1.27 (0.58–2.76)	0.55	46 (33.6)	38 (27.8)	1.82 (0.94–3.50)	0.07
RP-A1A2	11 (11.5)	16 (16.7)	0.62 (0.23–1.67)	0.35	26 (19.0)	28 (20.4)	1.39 (0.67–2.89)	0.37
RP-A2A2	–	–	–	–	1 (0.7)	0 (0.0)	–	
PP-A1A1	11 (11.5)	13 (13.5)	0.77 (0.28–2.11)	0.60	18 (13.1)	13 (9.5)	2.08 (0.87–4.95)	0.1
PP-A1A2	8 (8.3)	13 (13.5)	0.56 (0.19–1.64)	0.28	15 (11.0)	12 (8.8)	1.88 (0.76–4.64)	0.17
PP-A2A2	3 (3.1)	4 (4.2)	–		5 (3.6)	5 (3.6)	–	
p.R72P-r.13494g>a								
RR-GG	21 (21.9)	19 (19.8)	Reference		26 (19.0)	40 (29.2)	Reference	
RR-GA	0 (0.0)	1 (1.0)	–		0 (0.0)	1 (0.7)	–	
RP-GG	34 (35.4)	26 (27.1)	1.18 (0.53–2.64)	0.68	42 (30.6)	35 (25.6)	1.85 (0.95–3.60)	0.70
RP-GA	18 (18.8)	20 (20.8)	0.81 (0.33–1.98)	0.65	31 (22.6)	31 (22.6)	1.54 (0.76–3.10)	0.23
RP-AA	1 (1.0)	0 (0.0)	–		–	–	–	
PP-GG	9 (9.4)	10 (10.4)	0.81 (0.27–2.43)	0.71	14 (10.3)	14 (10.3)	1.54 (0.63–3.75)	0.34
PP-GA	9 (9.4)	16 (16.7)	0.51 (0.18–1.42)	0.19	20 (14.6)	11 (8.0)	2.80 (1.15–6.79)	0.02
PP-AA	4 (4.2)	4 (4.2)	–		4 (2.9)	5 (3.6)	–	
PIN3-r.13494g>a								
A1A1-GG	64 (66.7)	55 (57.3)	Reference		80 (58.4)	82 (59.9)	Reference	
A1A1-GA	9 (9.4)	7 (7.2)	1.11 (0.39–3.16)	0.86	10 (7.3)	8 (5.8)	1.28 (0.48–3.41)	0.62
A1A1-AA	1 (1.0)	0 (0.0)	–		–	–	–	
A1A2-GA	17 (17.7)	30 (31.3)	0.49 (0.24–0.98)	0.04	2 (1.4)	7 (5.1)	–	
A1A2-AA	2 (2.1)	0 (0.0)	–		39 (28.5)	35 (25.6)	1.14 (0.66–1.98)	0.64
A2A2-GA	1 (1.0)	0 (0.0)	–		2 (1.5)	0 (0.0)	–	
A2A2-AA	2 (2.1)	4 (4.2)	–		4 (2.9)	5 (3.6)	–	
p.R72P-PIN3-r.13494g>a								
RR-A1A1-GG	21 (21.9)	19 (19.8)	Reference		26 (19.0)	39 (28.5)	Reference	
RR-A1A2-GG	–	–	–	–	0 (0.0)	1 (0.7)	–	
RR-A1A2-GA	0 (0.0)	1 (1.0)	–		0 (0.0)	1 (0.7)	–	
RP-A1A1-GG	34 (35.4)	26 (27.1)	1.18 (0.53–2.64)	0.68	41 (30.0)	31 (22.6)	2.0 (1.0–3.92)	0.04
RP-A1A1-GA	8 (8.3)	4 (4.2)	1.81 (0.47–6.99)	0.39	5 (3.6)	7 (5.1)	–	
RP-A1A2-GA	10 (10.4)	16 (16.7)	0.57 (0.21–1.54)	0.26	1 (0.7)	4 (2.9)	–	
RP-A1A2-AA	1 (1.0)	0 (0.0)	–		25 (18.3)	24 (17.5)	1.56 (0.74–3.30)	0.24
PP-A1A1-GG	9 (9.4)	10 (10.4)	0.81 (0.27–2.43)	0.71	1 (0.7)	0 (0.0)	–	
PP-A1A1-GA	1 (1.0)	3 (3.1)	–		13 (9.5)	12 (8.8)	1.63 (0.64–4.11)	0.30
PP-A1A1-AA	1 (1.0)	0 (0.0)	–		5 (3.6)	1 (0.7)	–	
PP-A1A2-GA	7 (7.2)	13 (13.5)	0.49 (0.16–1.48)	0.20	1 (0.7)	2 (1.5)	–	
PP-A1A2-AA	1 (1.0)	0 (0.0)	–		14 (10.3)	10 (7.4)	2.1 (0.81–5.44)	0.12
PP-A2A2-GA	1 (1.0)	0 (0.0)	–		1 (0.7)	0 (0.0)	–	
PP-A2A2-AA	2 (2.1)	4 (4.2)	–		4 (2.9)	5 (3.6)	–	

OR, odds ratio; CI, confidence interval.

Further, we examined the combined effects of *TP53* polymorphisms in context of their haplotypes. R-A1-P-A-G haplotype was the most common in both oesophageal cancer patients and controls in the present study. Similarly, R-A1-G haplotype of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphism has been documented as most common haplotype in Russian diffuse large B-cell lymphoma patients (Voropaeva *et al*. 2014). We observed that P-A2-P-A-A haplotype of p.R72P, PIN3 Ins16bp, p.P47S, p.R213R and r.13494g>a polymorphisms of *TP53* was marginally associated with reduced EC risk in male patients. Association of few *TP53* haplotypes with cancer risk has been studied in various cancers but until now, there is no published study on *TP53* haplotypes in oesophageal cancer. A previous study from India had reported a modest risk of oral (Mitra *et al*. 2005a) and cervical cancer (Mitra *et al*. 2005b) in patients with R-A1-A haplotype of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphisms. Another study from western India on oral cancer had reported that P-A2-G haplotype combination of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphisms was associated with increased risk of oral cancer while P-A2-A haplotype was associated with

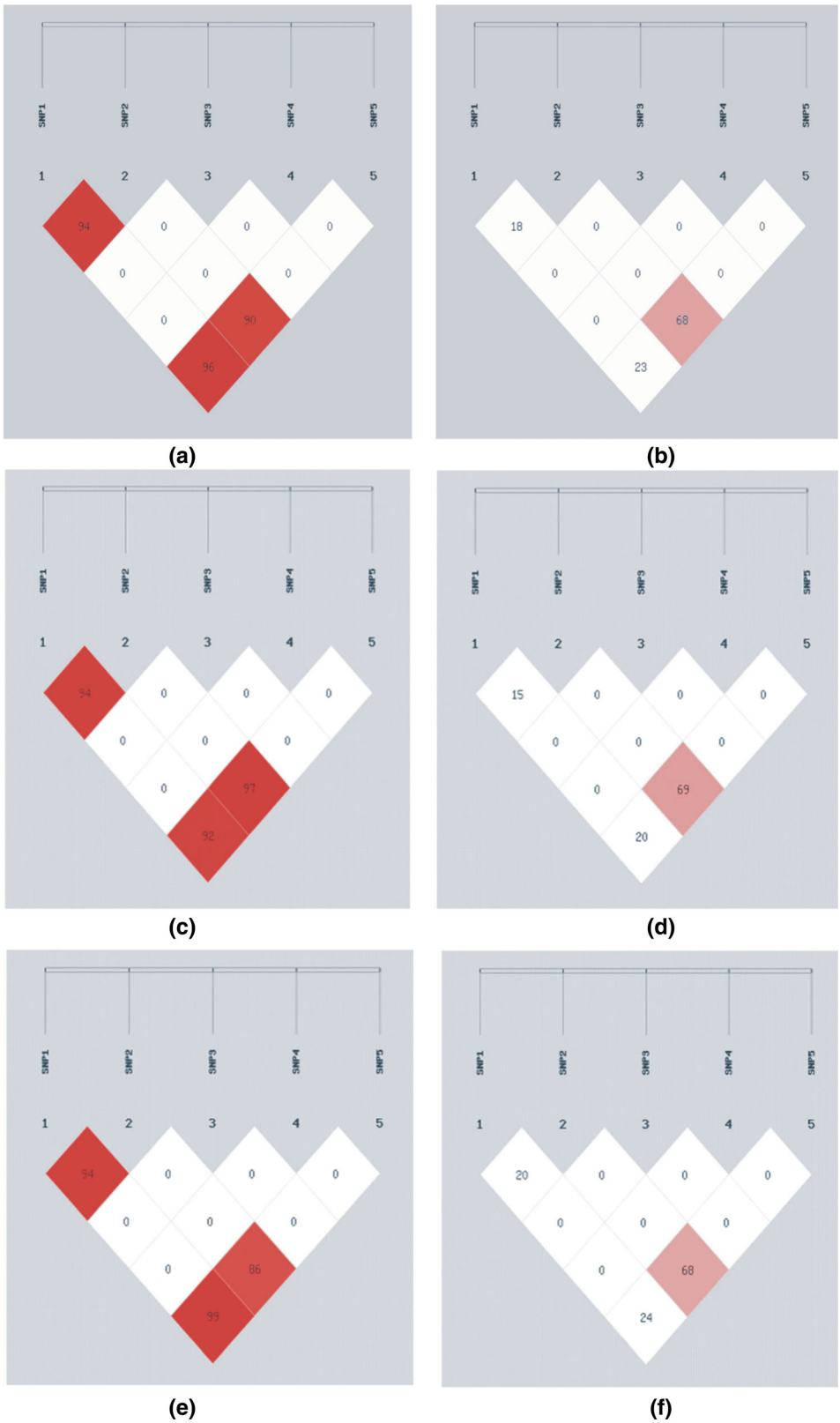

Figure 1. LD plot of five *TP53* polymorphisms in oesophageal cancer patients based on D′ and r^2. (a, b) Total, (c, d) males, (e, f) females. SNP1-p.R72P, SNP2-PIN3 Ins16bp, SNP3-p.P47S, SNP4-p.R213R and SNP5-r.13494g>a.

Table 6. Distribution of *TP53* haplotypes in oesophageal cancer patients and controls.

Haplotype combination	Patients (%)	Controls (%)	χ^2	OR (95%CI)	*P* value
Total					
R-A1-P-A-G*	46.6	49.1	0.70	Reference	
R-A2-P-A-G	0.3	0.4	–	–	–
R-A2-P-A-A	0.0	0.3	–	–	–
P-A1-P-A-G	31.7	28.5	1.05	1.16 (0.87–1.54)	0.31
P-A1-P-A-A	46.0	33.0	1.13	1.43 (0.74–2.80)	0.29
P-A2-P-A-G	9.0	1.2	–	–	–
P-A2-P-A-A	15.6	17.2	0.49	0.88 (0.62–1.25)	0.48
Male					
R-A1-P-A-G	48.6	44.0	0.93	Reference	
R-A1-P-A-A	0.9	0.0	–	–	–
R-A2-P-A-A	1.0	0.8	–	–	–
P-A1-P-A-G	31.6	32.5	0.02	0.97 (0.63–1.49)	0.88
P-A1-P-A-A	5.9	3.6	1.12	1.67 (0.64–4.39)	0.29
P-A2-P-A-G	0.6	0.0	–	–	–
P-A2-P-A-A	12.5	19.0	3.03	0.61 (0.35–1.07)	0.08
Female					
R-A1-P-A-G	45.1	52.7	3.71	Reference	
R-A2-P-A-G	0.5	0.5	–	–	–
P-A1-P-A-G	31.8	25.7	2.29	1.33 (0.92–1.94)	0.13
P-A1-P-A-A	37.0	30.0	0.19	1.23 (0.48–3.15)	0.66
P-A2-P-A-G	1.0	2.1	–	–	–
P-A2-P-A-A	17.8	16.0	0.27	1.13 (0.72–1.76)	0.61

*p.R72P-PIN3 Ins16bp-p.P47S-p.R213R-r.13494g>a.

decreased risk (Patel *et al*. 2013). A probable association of P–S haplotype combination of p.R72P and p.P47S polymorphisms with increased susceptibility to colorectal cancer has been reported in south Indians (Singamsetty *et al*. 2013).

A protective effect of R-A1-A haplotype combination of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphisms has been documented in breast (Sjalander *et al*. 1995) as well as in colorectal cancer (Sjalander *et al*. 1996). The P-A2-A haplotype combination of p.R72P, PIN3 Ins16bp and r.13494g>a polymorphisms have been significantly associated with the lung cancer risk (Wu *et al*. 2002). Haplotypes of rare allele of PIN3 Ins16bp and r.13494g>a polymorphism were slightly associated with increased risk of oral cancer in Taiwanese patients (Hsieh *et al*. 2005). A1-P haplotype of PIN3 Ins16bp and p.R72P polymorphism has been associated with increased risk of developing breast or ovarian cancer in individuals aged below 35 years (Osorio *et al*. 2006). A2–R haplotype combination of PIN3 Ins16bp and p.R72P polymorphism was associated with increased breast cancer risk in Turkish (Buyru *et al*. 2007) and Tunisian patients (Trifa *et al*. 2010). Increase in rare alleles of PIN3 Ins16bp and r.13494g>a polymorphism has been associated with decreased level of apoptosis (Wu *et al*. 2002). Rare allele of PIN3 Ins16bp polymorphism has been reported to be associated with an increased risk of colorectal cancer and reduced basal levels of p53 mRNA in lymphoblastoid cell lines (Gemignani *et al*. 2004). No association of haplotypes of PIN3 Ins16bp and p.R72P polymorphisms was observed in Chinese breast cancer patients (Hao *et al*. 2018). Association of A2-C-C-G haplotype of PIN3 Ins16bp, p.R72P, rs12947788 and rs17884306 polymorphisms of *TP53* with an increased risk and the haplotype A1-C-C-G with a decreased risk has been reported in Czech colorectal (Polakova *et al*. 2009), pancreatic (Naccarati *et al*. 2010) and breast cancer patients (Vymetalkova *et al*. 2015).

The presence of particular variant of different *TP53* polymorphisms could be responsible for the treatment response or treatment failure in cancer patients. As therapy response varies according to the status of *TP53* as reported in various cancers (Bergamaschi *et al*. 2003; Tommiska *et al*. 2005; Xu *et al*. 2005; Toyama *et al*. 2007; Huang *et al*. 2008; Kim *et al*. 2009; Rodrigues *et al*. 2013; Zha *et al*. 2016). Identification of correlation between *TP53* haplotypes and particular therapy may help in better selection of personalized treatment of patients.

In the present study, R-A1-P-A-G haplotype was the most common in both oesophageal cancer patients and controls whereas the frequency of P-A1-P-A-A haplotype was higher in female group. Here for the first we report the moderate LD between PIN3 Ins16bp and r.13494g>a intronic polymorphisms of *TP53* and association of *TP53* polymorphisms haplotypes in oesophageal cancer. Replication of these findings in independent cohorts may be insightful for the role of *TP53* in oesophageal cancer pathogenesis.

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