RESEARCH ARTICLE

Association of TP53 codon 72 polymorphism in women suffering from endometriosis from Lahore, Pakistan

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Abstract

Objective: To investigate TP53 gene codon 72 polymorphism in women with endometriosis and compare it with healthy samples.

Methods: This case-control study was carried out at Jinnah Hospital, Services Hospital and Sheikh Zayed Hospital, Lahore, Pakistan, from 2014 to 2016, and comprised patients with endometriosis and healthy controls. SPSS 21 was used for statistical analysis.

Results: Of the 176 participants, 88(50%) were healthy controls and 88(50%) were endometriosis patients. The observed genotype frequencies for controls and patients were 14(15.9%) and 31(35.3%) for proline/proline, 46(52.3%) and 35(39.8%) for proline/arginine, and 28(31.8%) and 22(25%) for arginine/arginine, respectively. The association of different genotypes was not significant in patients with moderate-to-severe endometriosis (p=0.574). The presence of pro/pro genotype enhanced the chances/odds of getting the disease (p<0.05). However, the risk further increased with the advancement of age, particularly in the 27-46 age group (p<0.05).

Conclusion: In Pakistani women the association of TP53 gene codon 72 arginine/proline polymorphism was present.

Keywords: TP53 gene, Endometriosis, Codon 72, Pakistani population, Cell cycle. (JPMA 68: 224; 2018)

Introduction

Endometriosis is the presence of endometrial like tissue, glands and stroma outside the uterus, mostly affecting the pelvic organs. Since the aetiology of endometriosis is not yet known, many environmental, dietary and genetic factors have been found to modulate it. Various animal model studies revealed that high serum levels of polychlorinated biphenyls (PCBs) favoured endometriosis development and the disease severity was found in direct correlation with serum PCB levels.[1] Similarly, the use of trans-fat increases the risk of endometriosis while omega 3 oils decrease the risk.[2] Other risk factors of endometriosis are early menarche, nulliparity, prolonged and frequent menstrual cycles, heavy menstrual bleeding and keeping intra-uterine contraceptive devices for long periods.[3,4] The common disease symptoms include dysmenorrhoea, dysuria, dyschezia, dyspareunia and infertility. The symptoms of extrapelvic endometriosis include cyclical haemoptysis, cyclical bleeding from caesarean scar and cyclical haematuria.[5]

The renowned complications include compression symptoms, cancer development, especially ovarian carcinomas in case of ovarian endometriosis, cyst rupture and occasionally death.[6] Endometriosis can recur even after surgical resection, which explains the high morbidity associated with the disease as far as the physical and mental health status is concerned.[7] In Pakistani women, endometriosis-based infertility is 24% compared to infertility associated with other gynaecological pathologies.[8] Endometriosis affected women and their families are found to be at great risk of other cancers like breast cancer, endometrial cancer, non-Hodgkin lymphoma and melanoma.[9]

TP53 is a tumour suppressor gene located on chromosome 17p13.1.[10] It controls the regulation of cell growth and cell cycle by inducing apoptosis or blocking the cell cycle in response to deoxyribonucleic acid (DNA) damage. To maintain tissue homeostasis, apoptosis plays a key role by removing dysfunctional cellular debris especially in ectopic endometrial foci.[11] A total 14 polymorphisms of TP53 have been reported to date.[12] The most important one is rs1042522 which lies in exon 4 codon 72 region. This proline (pro) rich region is primarily responsible for the execution of apoptotic property of TP53 gene. It is a functional polymorphism which is found on exon 4 and causes the substitution of proline with arginine (arg) residue at the regulatory portion of TP53 gene, resulting in altered regulation of apoptosis. Different studies have established a definite association of TP53 codon polymorphism with endometriosis. The current study was planned to test the hypothesis

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thatTP53 gene codon 72 polymorphism (Pro72Arg) is associated with endometriosis and affects the severity of the disease in Pakistani women.

Patients and Methods

This case-control study was carried out at Jinnah Hospital, Services Hospital and Sheikh Zayed Hospital, Lahore, Pakistan, from 2014 to 2016, and comprised patients with endometriosis and healthy controls.

The sample size was calculated with the confidence level of 95% and taking the case-control population proportions of 0.05 and 0.15, respectively, based on an earlier study.[14] The selection of patients was done on laparoscopy and on histological sections, whereas the control group comprised healthy women who had undergone caesarean section whereby pelvic endometriosis was ruled out. Subjects with 17-46 years of age (safe range between the age of menarche and menopause), married for more than one year (infertility is labelled usually 1-2 years after marriage), nulliparous/multiparous, primary/secondary infertility were selected. Patients taking any treatment for infertility, e.g. in vitro fertilisation (IVF), laparotomy/laproscopy for any other condition more than two times, history of ectopic pregnancy, taking any hormones, combined oral contraceptives (COCs), or gonadotropin-releasing hormone (GnRH) analogue, history of tuberculosis (abdomen) or anti-tuberculosis therapy, thyroid dysfunction, and with any malignancy were excluded from the study. The control subjects with the same defined criteria of age, marital status and parity as cases who had undergone caesarean section due to foetal stress were selected, whereas subjects with history of outflow tract anomalies/obstruction or abdominal tenderness were excluded. About 5ml blood was drawn from each subject in ethylenediaminetetraacetic acid (EDTA)-coated vacutainer tubes and stored at 4°C until DNA isolation was commenced. It was ensured that all procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the World Medical Association (WMA) Declaration of Helsinki, 2013. The institutional review board and ethical committee of the University of Health Sciences, Lahore, and respective hospitals approved the study. Informed consent was obtained from all the participants.

The genomic DNA was isolated using phenol-chloroform extraction protocol with some modifications. Amplification of codon 72 polymorphism was carried out by the set of primers.[13] The constituents of 20µl polymerase chain reaction (PCR) reaction mixture were: 50ng DNA, 2mM magnesium chloride (MgCl2), 2.5 m Mdeoxynucleotides (dNTPs), 10X PCR buffer, 0.5µM forward and reverse primer and 5U Taq DNA polymerase. The thermal cycling conditions were set as follows: initial denaturation at 94°C for 2 minutes followed by 35 cycles of 94°C for 30 seconds; 60°C for 30 seconds and 72°C for 1 minute with final extension at 72°C for 5 minutes. Amplified product of 396bp of p53 gene was analysed for codon 72 polymorphism by the restriction fragment length polymorphism (RFLP) technique using 4U of BstUI (Bsh1236I) restriction enzyme (Thermo Scientific, United States) in thermal cycler at 60°C for 16 hours. Restriction products were analysed at 2.5% agarose gel where the uncut band of 396 bp showed the presence of proline allele. On the contrary, two fragments of 165bp and231bp depicted the presence of arginine allele. The heterozygous arginine/proline allele was confirmed by the presence of all three aforementioned fragments.

SPSS 21 was used for statistical analysis. $P \leq 0.05$ was considered statistically significant. General demographics were summarised in the form of mean and standard deviation (SD) for scale variables while categorical data was summarised as frequency percentages. Pearson's chi-squared (χ^2) was used to assess their association of various parameters with disease status. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic-regression models. Allele frequency of p53 codon 72 polymorphism was checked in overall study subjects and then in controls and cases for deviation from Hardy-Weinberg equilibrium (HWE) using Online Encyclopaedia for Genetic Epidemiology (OEGE).To test the association of p53 codon 72 polymorphism with the disease, multiple inheritance models (co-dominant, dominant, recessive, over-dominant, and log-additive) were tested by logistic regression using online software SNPStats. Moreover, for these inheritance models, odds ratio with 95% CI was also calculated with and without the presence of other biological covariates. In order to choose the best inheritance model, the models created by SNPStats were tested against the most general, i.e. co-dominant model, by a goodness-of-fit likelihood ratio test (LRT) and then evaluated by Akaike information criterion (AIC) and Bayesian information criterion (BIC). The model with the lowest AIC and BIC values was chosen for testing its association with characteristics of the females with endometriosis.

Results

Of the 176 participants, 88(50%) were healthy controls

Table-1: The studied parameters of present case control study.

Characteristics		Subjects n=176 (%)	Endometriosis n=88 (%)	No endometriosis n=88 (%)	p-Value	OR [95% CI]
Age						
	17-26 years	79 (44.9)	30 (34.1)	49 (55.7)	--	--
	27-36 years	86 (48.9)	49 (55.7)	37 (42.0)	0.015	2.163 [1.160 - 4.035]
	37-46 years	11 (6.3)	09 (10.2)	02 (2.3)	0.014	7.350 [1.487 - 18.337]
Age of Menarche						
	< 12 years	22 (12.5)	10 (11.4)	12 (13.6)	0.649	0.812 [0.331 - 1.991]
	> 12 years	154 (87.5)	78 (88.6)	76 (86.4)		
Parity						
	Multiparous	64 (36.4)	24 (27.3)	40 (45.5)	--	--
	Primiparous	51 (29.0)	03 (3.4)	48 (54.5)		
	Nulliparous	61 (34.7)	61 (69.3)	00 (0)		
Blood Groups						
	A+	33 (18.8)	13 (14.8)	20 (22.7)	--	--
	B+	47 (26.7)	26 (29.5)	21 (23.9)		
	AB+	17 (9.7)	07 (8.0)	10 (11.4)		
	O+	68 (38.6)	35 (39.8)	33 (37.5)		
	O-	11 (6.2)	07 (7.9)	04 (4.5)		

OR: Odds Ratio
CI: Confidence Interval.

Table-2: Genotypes of p53 codon 72 polymorphism by PCR-RFLP in endometriosis (88) and non-endometriosis groups (88).

Genotypes/Alleles	No Endometriosis n=88 (%)	Endometriosis n=88 (%)	p-Value	OR crude [95% CI]	p-Value adjusted*	OR Adjusted* [95% CI]	AIC*	BIC*
Genotypes								
Co-Dominant Model								
Arg/Arg	28 (31.8)	22 (25.0)	1.00	1.00	238.9	254.8		
Arg/Pro	46 (52.3)	35 (39.8)	0.929	0.968 [0.476 - 1.917]	0.869	0.941 [0.456 - 1.943]		
Pro/Pro	14 (15.9)	31 (35.2)	0.016	2.818 [1.213 - 6.545]	0.018	2.806 [1.191 - 6.610]		
Dominant Model								
Arg/Arg	28 (31.8)	22 (25.0)	0.317	1.00	0.349	1.00	244.8	257.5
Arg/Pro + Pro/Pro	60 (68.2)	66 (75.0)	1.400 [0.724 - 2.705]	0.726 [0.371 - 1.419]				
Recessive Model								
Arg/Arg + Arg/Pro	74 (84.1)	57 (64.8)	0.004	1.00	0.004	1.00	237	249.6
Pro/Pro	14 (15.9)	31 (35.2)	2.875 [1.400 - 5.903]	2.912 [1.397 - 6.071]				
Overdominant Model								
Arg/Arg+ Pro/Pro	42 (47.7)	53 (60.2)	0.096	1.00	0.084	1.00	242.7	255.4
Arg/Pro	46 (52.3)	35 (39.8)	0.603 [0.331 - 1.096]	0.590 [0.321 - 1.083]				
Log-additive Model	----	0.018	1.640 [1.080 - 2.480]	0.021	1.632 [1.073 - 2.490]	240.3	253	
Alleles								
Arg	102 (57.9)	79 (44.9)	0.018	1.00	0.018	1.00	--	--
Pro	74 (42.1)	97 (55.1)	1.692 [1.110 - 2.580]	1.692 [1.110 - 2.580]				

* Adjusted based on Age of study subjects and Age of Menarche
PCR: Polymerase chain reaction
RFLP: Restriction fragment length polymorphism
OR: Odds ratio
CI: Confidence interval
Arg: Arginine
Pro: Proline
AIC: Akaike information criterion
BIC: Bayesian information criterion.

Table-3: The Odds ratio for various studied parameters in association with three studied genotypes.

Parameters	Genotype [n (%)]		p-Value*	ODDS ratio [95% CI]
	WW & MM	MM		
Endometriosis				
Grade I & II	43 (75.4)	25 (80.6)	0.574	1.00
Grade III & IV	14 (24.6)	06 (19.4)		0.737 [0.251- 2.162]
Infertility				
Primary	46 (80.7)	22 (71.0)	0.304	1.00
Secondary	11 (19.3)	09 (29.0)		1.711 [0.619- 4.730]
Age of Menarche				
Greater than 12 Years	50 (87.7)	28 (90.3)	0.710	1.00
Less than 12 Years	07 (12.3)	03 (9.7)		0.765 [0.183- 3.196]
Parity Status				
Multiparous &Primiparous	18 (31.6)	09 (29.0)	0.804	1.00
Nulliparous	39 (68.4)	22 (71.0)		1.128 [0.434 - 2.934]

* Cells with count less than 05 have p-values calculated using Fisher's Exact Test.
CI: Confidence interval.

Table-4: Comparison of TP53 gene codon 72 polymorphism in the present study population (Lahore) with the already available data from different populations.

Investigator	Population	Endometriosis				No endometriosis				Association status	Polymorphism
		n	arg/arg (%)	arg/pro (%)	pro/pro (%)	n	arg/arg (%)	arg/pro (%)	pro/pro (%)		
Chang, et al., 2002[14]	Chinese	118	10.2	66.9	22.9	140	30.7	50	19.3	Yes	pro/pro
Hur, et al., 2002[23]	Korean	74	18.9	62.2	18.9	93	12.9	75.2	11.9	No	Non-significant
Lattuada, et al., 2004[10]	Italian	151	55.6	39.7	4.6	152	59.9	30.9	9.2	No	Non-significant
Omori et al., 2004[15]	Japanese	111	35.2	48.5	16.2	180	39.4	41.7	18.9	No	Non-significant
Hsieh and Lin, 2006[13]	Taiwanese	148	9.5	66.2	24.3	150	31.7	49.3	19.3	Yes	pro/pro
Vietri et al., 2007[25]	Italian white	104	61.5	34.7	3.8	88	54.5	40.9	4.6	No	Non-significant
Ammendola et al., 2008[24]	Caucasian Italian	129	45.7	44.2	10.1	147	46.3	40.1	13.6	No	Non-significant
Govatati et al., 2012[18]	Indian	721	28.6	51.8	19.6	500	28.2	51.2	20.6	No	Non-significant
Dastjerdi, et al, 2013[17]	Iran	90	28.9	55.6	15.6	90	42.2	54.4	3.3	Yes	Pro/pro
Present study 2017	Pakistani	88	25.0	39.8	35.2	88	31.8	52.3	15.9	Yes	pro/pro

Arg: Arginine
Pro Proline.

and 88(50%) were patients. It was observed that with the advancement of age the odds for disease development increased significantly (p=0.014). Moreover, high percentage of nulliparous women, i.e. 61(69.3%), among the endometriosis group supported the high occurrence of infertility among afflicted women (Table-1).

The genotype frequencies among the endometriosis group of arg/arg (homozygous), arg/pro (heterozygous) and pro/pro (homozygous) were 22(25%), 35(39.8%) and 31(35.2%), respectively. The genotype frequencies of arg/arg (homozygous), arg/pro (heterozygous) and pro/pro (homozygous) were 28(31.8%), 46(52.3%) and 14(15.9%), respectively. The obtained genotype frequencies highlighted that odds ratio increased from 0.968 (95% CI=0.476-1.917) to 2.818 (95% CI=1.213-6.545) for pro/pro variant for disease development. The allelic frequency of proline was significantly high (p=0.01) in endometriosis group compared to arginine allele which was more in non-endometriosis group (Table-2).

About 68(77.3%) patients showed primary infertility and grade I and II endometriosis stage. Their transvaginal scan (TVS) showed that about 70(79.5%) patients had bilateral endometriotic cyst (Table-3).

The influence of genotype markedly differed with various associated risk factors for endometriosis. Being arginine heterozygous or proline homozygous posed more odds for endometriosis as far as early menarche (age <12 years) OR=1.3 (95% CI=0.270 - 7.045) was concerned. Also, for parity status, nulliparity imparted 0.5 times odds OR=0.588 (95% CI=0.192 - 1.804) for endometriosis.

The overall results of the distribution of p53 codon 72 polymorphism in endometriosis and control group among various populations worldwide were collated. The data had been supported by two meta-analysis studies whereby the role of p53 codon 72 polymorphism in causing endometriosis was verified in Asian ethnicity, and results obtained from the present study suggested the same (Table-4).

Discussion

Endometriosis, a notable fertility disorder of women, is not only driven by hormonal factors but genotypic constitution like TP53 codon 72 polymorphism also plays its part. Two variants derived from the substitution of single nucleotide in codon 72, resulting in proline or arginine, have been described in TP53 gene. The allele frequency of TP53 gene codon 72 polymorphism has been studied in many populations worldwide with variable results, mainly due to racial variations. The presence of arginine homozygosity is reported to give protection against endometriosis, whereas arginine/prolineheterozygosity and prolinehomozygosity is reported to be positively associated with endometriosis.[13,14] Contrary to this, another study on Japanese population reported no association of TP53 gene codon 72 polymorphism with endometriosis.[15]

The present study involved the investigation of genotype and allele frequencies of TP53 codon 72 polymorphism in patients of endometriosis and healthy women. It was found that pro/pro (homozygous) genotype was not only more frequently occurring among patients of endometriosis but also showed 2.8 times odds for the development of endometriosis OR=2.806 (95% CI =1.91-6.610) compared to 0.9 times odds forarg/pro heterozygous OR=0.941 (95% CI=0.456-1.943) for having endometriosis. These results are consistent with an earlier study performed on Chinese population.[13] Accordingly it can be said that arginine homozygosity had a protective role while prolinehomozygosity and arginine heterozygosity increased the susceptibility towards endometriosis.

The higher frequency of proline allele (55.1%) among women having endometriosis compared to 42.1% in non-endometriotic women are in agreement with a 2006study by Hsieih and Linon Taiwanese population, where almost the same frequency of proline allele was reported in women having endometriosis (57.4 %).[14] The frequencies of both alleles in our study were not only statistically significant (p=0.018) but also revealed 1.6 times odds for developing endometriosis for being proline homozygous OR=1.692 (95% CI=1.110-2.580).

The dominance of arginine allele (57.9%) among healthy women in our study is supported by a study on Indian women where the frequency of arginine allele was 56% in healthy females as compared to breast cancer patients,[16] with almost the same genotypic constitution of residents of the subcontinent.

The findings of our study are consistent with another data presented from neighbouring Iran, with a positive association of TP53 codon 72 polymorphism and endometriosis. In the present study we observed 2.8 times odds [OR =2.875 (95% CI=1.400-5.903)] contributed by proline allele in the dominant model, similar to5.3 times odds [OR=5.34 (95% CI=1046-19.29)] imparted by proline genotype in Iranian women.[17]

Our data revealed the impact of allele on increasing odds of endometriosis when different statistical models were assessed. Proline allele, even in the recessive model, contributed 2.8-fold risk of endometriosis [OR =2.875 (95% CI=1.400-5.903)]. In the dominant model, the odds shared by proline allele were 1.4 times (OR=1.400: 95% CI=0.724-2). These results are in accordance with a study on Indian population depicting the role of proline allele in increasing the risk of endometriosis in either model. The study reported proline allele contribution in endometriosis risk with OR=1.06 (95% CI=0.801-1.415) in the dominant model while OR=1.021 (95% CI=0.792-1.314) in the recessive model.[18]

TP53 gene codon 72 polymorphism has also been reported to be linked with the severity of endometriosis. Studies on two different populations have reported that the presence of proline at TP53 codon 72 was associated with minimal or mild endometriosis,[19,20] whereas in Italian population the presence of proline has been found to be associated with severe form of endometriosis.[10] The studied population in the current study was also categorised on the basis of disease severity, and 81.1% of population with homozygous arginine had grade I and II disease while only 18.2% were in grade III and IV. The heterozygous arg/pro75.8% and homozygous pro/pro were in grade I and II and 24.2% in grade III and IV (p=0.77), OR=1.44 (95% CI =0.425 - 4.883). These observations are in concordance with a study of Kang et al.(2004)[19] who reported that patients with homozygous proline are more prone to grade I and II of endometriosis (OR=2.75, p=0.013). Moreover, our reported results are also in contradiction to a study on Brazilian population where 63.63 % arg/pro and pro/pro

women were reported to have grade III and IV disease (p=0.6115).[20]

Among various risk factors, advanced age was strongly correlated with endometriosis in the present study. According to our findings, there were 2 times odds for endometriosis [OR=2.163 (95% CI= 1.160 - 4.035)] for age group 27-36 years while for age group 37-46 years odds for having endometriosis increased to 7 times [OR=7.350 (95% CI= 1.487 - 18.337)]. These observations are strongly in agreement with a study from the United States where advanced age is a risk factor for endometriosis with OR= 2.0 (95% CI=1.1-3.7).[4] Endometriosis-associated primary and secondary infertility observed in this study was 77.3% and 22.7%, respectively, which is partially in agreement with another study.[8]

Our research data explained that in the dominant model the odds shared by proline allele were 1.4 times (OR=1.400: 95% CI=0.724-2). These results are in agreement with meta-analysis results where the individuals carrying proline allele (stratified analysis) in a dominant model have 2.5 times odds for endometriosis [OR=2.595 (95% CI=1.005-6.702)] (p=0.049). Therefore, our findings of association of TP53 codon 72 polymorphism with endometriosis in Asians is clearly in agreement with other studies.[21] The authenticity of our first-ever reported results from Lahore, Pakistan, revealing the association of TP53 codon 72 polymorphism and endometriosis is favoured by another research particularly commenting on the positive relationship between TP53 codon 72 polymorphism in a pooled analysis, showing dominant model with OR=0.827 (95% CI=0.712-0.960).[22]

Although this research was conducted on a small scale, the basic data of genetic constitution of local Pakistani women of reproductive age group experiencing infertility is the first of its kind, which can serve as grounds for more diverse and advanced research.

Conclusion

The association of TP53 gene codon 72 arg/pro polymorphism was present in Pakistani women, and proline allele frequency had high incidence among recruited patients of endometriosis, but no significant association between severity of endometriosis and TP53 gene codon 72 arg/pro polymorphism was observed. The presence of pro/pro genotype enhances the chances/odds of contracting the disease. However, the risk is further increased with the advancement of age, particularly inthe27-46 age group. Moreover, Asian ethnicity is a well-known recognised risk factor for endometriosis.

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Conflict of Interest: None.

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