ORIGINAL ARTICLE

Association of Genetic Variants in XPC and XPG Genes with Cervical Cancer Risk in a Rural Population: A Hospital Based Case Control Study

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Abstract:

Background: Cervical cancer is a major concern of health risk in urban and rural parts of India.. *Aim and Objectives:* This study was aimed to find out frequency of polymorphisms in DNA repair genes including Xeroderma pigmentosum complementation group C (XPC) and Xenoderma pigmentosum complementation group G (XPG) in patients of cervical cancer from Maharashtra and to evaluate their association with risk of cervical cancer. *Materials and Methods:* We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to examine gene polymorphisms in 350 patients with cancer of cervix and 400 age and sex matched normal controls. *Results:* The results obtained indicated that there was no significant difference in the genotype distribution between cervical cancer patients and controls for XPC Lys939Gln, -371promoter and XPG His 1104 Asp. The result showed that genotype frequencies of XPC Val 499 Arg of codon 499 in exon 15 (OR=4.26; 95% CI= (3.007-6.03); p= <0.0001) were increased significantly. *Conclusion:* This study indicates that polymorphisms in Val499Arg haplotype of XPC gene appear to influence genetic susceptibility of individual to cervical cancer in Maharashtrian patients.

Keywords: Cervical cancer**,** Genetic polymorphism, XPC, XPG, PCR-RFLP

Introduction:

Cervical Cancer (CC) is the second most common cancer among women worldwide and one of the most common causes of death among women in developing countries [1]. Approximately 500,000 cases of CC appear every year worldwide, of which eighty percent occur in developing countries where the highest incidence rates of CC are observed in Africa, Caribbean, South, Central and Southeast Asia [2]. In 2014, 122,844 women were diagnosed with cervical cancer and 67,477 deaths were reported in women because of this disease from different regions of India [3]. The etiologic factors involved in cervical carcinogenesis involve reproductive factors, early age of first intercourse, multiple pregnancies or sexual partners, infection with high risk Human Papilomavirus (HPV), association with other sexually transmitted diseases, smoking, alcohol ingestion, diet and use of oral contraceptives[4]. In Maharashtra, the risk of cervical cancer was noticed to be associated with increasing age, low education level, early age at first sexual intercourse and high-risk HPV [5]. Sometimes, exposure of individuals to the above said risk factors do not develop CC which suggests that there is something else which is involved in cervical carcinogenesis. Identification of involvement of genetic determinants in cervical carcinogenesis may contribute to understand mechanisms of cancer development.

Several DNA repair mechanisms such as Base Excision Repair (BER), Nucleotide Excision Repair (NER), Double Strand Repair (DSBR) and DNA Mismatch Repair (DMR) pathways are thought to play a crucial role in maintenance of genomic integrity and genetic stability. But, it is not yet clear which DNA repair mechanisms are most important for protection against DNA injury in case of cancer. Xenoderma pigmentosum, complementation group C (XPC) and Xenoderma pigmentosum, complementation group G (XPG) are major components of the NER pathway. The XPC gene uniquely involved in global genome repair and XPG gene expresses proteins having role in the NER pathway that can repair bulky lesions. Polymorphisms in the genome can confer genetic susceptibility to cancer in human. Hundreds of polymorphisms in DNA repair genes including XRCC, XPD, XPC and XPG which have been frequently studied and some of them were shown to be associated with significant cancer risk. Previous studies on XPC and XPG suggested that polymorphisms of those genes were associated with an increased risk of many human malignancies including stomach, prostate and colorectal cancer [6-8], but some of the studies produced contradictory or an inconclusive results in breast cancer [9-10]. Also, the earlier observations were not consistent in terms of their roles in CC susceptibility [11]. Few studies from Indian population revealed that polymorphisms in XPC and XPG genes may serve as risk factor for the development of CC but the records are not sufficient to prove the incident [12].

There are no published reports on the association between XPC and XPG variants and risk of CC in Maharashtra. In earlier studies we have reported that the polymorphisms in NER pathway gene including XPC plays important role in oral cancer where as neither XPC nor XPG is involved in breast carcinogenesis [13-14]. We hypothesized that the inherited polymorphisms in XPC and XPG may contribute to genetic susceptibility to CC in a rural population from south-western Maharashtra. To test this hypothesis, we conducted a hospital based case control study to investigate the polymorphisms in the two genes with the risk of CC development in the rural population.

Materials and methods

Study subjects

In a hospital based case-control study, study participants included 350 newly diagnosed CC patients and 400 healthy, cancer free, age matched females as controls. All cases ranged in age from 20-80 years (Mean ± SD) (48.67 ±13.78) were recruited immediately after being diagnosed during the year 2014-2017. Trained interviewers used a structured questionnaire to collect personal interview data from the participants regarding demographic factors and known risk factors.

Place of Study

This study was conducted in Krishna Institute of Medical Sciences "Deemed to be University" from Maharashtra state of India.

Selection of cases and controls

The diagnosis of CC was confirmed by colposcopy done at Department of Gynecology and Obstetrics of the Krishna Hospital & Medical Research Centre (KH&MRC) and cell cytology at the Department of Pathology of Krishna Institute of Medical Sciences. Controls were randomly selected from a group of women visiting to KH&MRC.

Inclusion & Exclusion criteria:

Relatives of cases or persons who had a prior history of cancer were excluded from the study. All patients and controls agreed to give written consent were included in this study.

Genomic DNA isolation from whole blood

Genomic DNA was extracted from 5mL of peripheral blood using Purelink genomic DNA extraction and purification Kit (Invitrogen, Thermo Fisher Scientific, California, USA) following the manufacturer's instructions.

Genotyping assays.

Genotyping of XPC and XPG were performed by PCR-RFLP methods with appropriate primer sets. The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: (A) XPC Val499Arg of codon 499 in the exon-8 SNP rs2228000 C>T), (B) XPC Lys939Gln of cd939in the exon15 SNP rs2228001 (A>C) (C) -371 Promoter region of XPC gene SNP: rs3731055 (G>A) and (D) XPG His 1104 Asp of codon 1104 in the exon-15 SNP (rs17655) (G>C). The primers selected to amplify the specific SNPs of interest were; Forward 5'-CGG CTC TGA TTT TGA GCT CTC C-3' Reverse 5'-GCT TGA AGA GCT TGA GGA TGG C-3' for codon 499; Forward 5'-GGA GGT GGA CTC TCT TCT GAT G-3', Reverse 5'-TAG ATC CCA GCA GAT GAC C-3' for codon 939; Forward 5'-CAG TTC CTT GTT TCC TTC AC-3', Reverse 5'-GTT TCC GGA GAT TGA CGT TG-3' for XPC -371 promoter, and (Forward 5′-5'-GAC CTG CCT CTC AGA ATC ATC-3' Reverse 5'-CCT CGC ACG TCT TAG TTT CC-3') for XPG codon 1104. The PCR amplifications were performed in separate reactions of 20 μL reaction volumes containing 200 ng of genomic DNA, 10 pmoles of each above mentioned primers, 200 μM each dNTPs, 10 mM Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl2 and 1 unit of Taq DNA polymerase (GeNei, Merck Biosciences, Bangalore, India). The reaction mixtures were subjected to PCR amplification with different PCR conditios in a Master Cycler Gradient PCR (Eppendorf). The PCR cycle conditions for amplification of XPC codon 499 of 210 bp, (denaturation at 95^0C- 5 min, 30 cycles of 95^0C- 20 sec, 55^0C- 20 sec, 72^0C- 20 sec and final extension at 72^0C- 10 min), XPC codon 939 of 765bp, 95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 52^0C- 45 sec, 72^0C- 30 sec, 72^0C- 5 min , XPC promoter -371 of 650 bp (95^0C- 5 min, 30 cycles of 95^0C- 30 sec, 51^0C- 30 sec, 72^0C- 45 sec and 72^0C- 10 min), and XPG codon 1104 of 271bp (95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 55^0C- 30 sec, 72^0C- 30 sec, 72^0C- 10 min). After performing PCRs for each of the reactions, the PCR products were analyzed by agarose gel electrophoresis. After confirmation of amplification of specific fragments, PCR products were digested overnight with the appropriate restriction enzymes (Fermentas, Thermo Fisher Scientific USA) at 37°C. 2 units of XbaI, HhaI, PvuII and NlaIII restriction enzymes were used respectively for digestion of PCR products of -371 XPC promoter, XPC codon 499, XPC codon 939 and codon 1104 of XPG. Digested PCR products were resolved on 2.0 % agarose (GeNei, Merck Biosciences, Bangalore, India) gel at 100 V for 30 min, stained with ethidium bromide and photographed with gel documentation system (BioRad Laboratories, California, USA).

Statistical analysis

The association between the XPC and XPG genotypes and risk of CC development were

studied using odds ratio (OR). Both the univariate and multivariate logistic regression analyses were employed to calculate the adjusted ORs and 95% confidence intervals (CIs) with adjustment of variables to determine the CC risk associated with genotypes. All statistical analyses were performed with SPSS version 11 software.

Ethics and biosafety

The study protocol was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences "Deemed to be University" for the use of human subjects in research.

Results

Characteristics of the subjects:

Total of 350 women cases with CC and 400 controls were selected to match these cases were assessed during this study. The mean ± SD age of cases and controls was 48.67 ± 13.78 (median: 50, range 25-75) and controls 46.37 ± 13.90 (median: 33.5 range 24-75) years respectively. The overall demographical details with characteristics of the study population including both CC cases and healthy controls were summarized in Table-1, which showed significant difference in the demographic characteristics except age of cancer occurrence (p=0.03) and dietary factors (p=0.59). There was no significant difference between cases and controls when we compared age at first pregnancy of cases (78%) and controls (45.25%)

Association XPC and XPG genotype variants with cervical cancer risk.

We determined the frequency of polymorphisms in XPC and XPG genes implicated in DNA damage repair in CC patients and matched controls in order to evaluate their association with the risk of CC. The distribution of the polymorphism Val499Arg of codon 499, Lys939Gln of codon 939 and promoter -371 of XPC and Asp1104Gln codon 1104 of XPG genes and concordance of the cases and controls are presented in Table-2.

Analysis of the Val499Arg, Lys939Gln and promoter -371 polymorphism in the XPC gene

We carried out an allelic association analysis for three SNPs (rs2228000, rs2228001 and rs3731055) in XPC gene and found that XPC Val499Arg was significantly associated with risk of CC. Genotype distributions in the cases and controls for the nonsynonymous polymorphisms in XPC are shown in table 2. When we studied substitution polymorphism, we found the frequency of XPC 21151CC wild type alleles at codon 499 of exon 8 was 20.6%, 21151CT heterozygote alleles was 16% whereas 21151TT homozygous variant allele was 63.4% in the studied cases where as that of the frequencies for the controls were 45.22, 22 and 32.7% for wild type heterozygous and homozygous variant type alleles. The logistic regression analysis revealed that TT homozygous allele (crude OR: 4.26, 95% CI: 3.007-6.03, p<0.0001) and heterozygote CT allele (OR: 1.59, 95% CI: 1.03-2.46 p<0.04) of Val499Arg at exon 8 ox XPC had significantly increased risk of CC. In contrast the XPC Lys939Gln genotype was not associated with CC risk (OR: 1.52, 95% CI: 0.89-2.61). The frequency of *XPC 33512AA* wild type alleles at codon 939 of exon 15 was 49.4%, 33512AC heterozygote alleles was 40.3% and for 33512CC homozygous alleles was 10.3% in the cases where that of the frequencies for the controls were 49.5, 43.75 and 6.75 % respectively.

Table 1: Distribution of Selected Demographic Variables of Cervical Cancer Cases and Healthy Controls

Variable	Cases N=350		Controls N=400		*P* Value based on $\chi 2$
Age (Mean ± SD) years	48.67 ±13.78		46.37 ± 13.90		
	No.	(%)	No.	(%)	
⩽ 50	215	61.40	284	71.00	0.003
51-60	59	16.90	69	17.20	
61-70	57	16.30	34	08.50	
>70	19	5.40	13	03.20	
Tobacco status					
Tobacco users	189	54.00	113	28.20	<0.001
Tobacco no users	161	46.00	287	71.80	
Age @ Ist Pregnancy (yrs)					
15-20	276	78.90	181	45.25	<0.001
21-25	73	20.90	178	44.50	
26-30	00	0.00	36	9.00	
31-35	01	0.20	05	01.25	
Diet					
Vegeterian	97	27.70	118	29.50	0.59
Mixed	253	72.30	282	70.50	
Education					
High School	139	39.71	108	27.00	<0.001
High School graduate (12 y)	24	06.86	49	12.25	
College /Graduate	43	12.29	129	32.25	
No School	144	41.14	114	28.50	
Family history of Cancer					
Yes	62	17.71	10	02.50	<0.001
No	288	82.29	390	97.50	

*: Indicates significant difference (p<0.001) between the cases and controls from studied population.

Table 2: The genotype frequencies of *XPC* and *XPG* gene variants in untreated CC patients and controls

GENE	Genotype	CASES (n= 350) (%)	CONTROL (n = 400) (%)	Odds' Ratio (95% CI)	*P* value	Adjusted Odds Ratio (95% CI)	*P* value
XPC Val499Arg Cd499 Exon8 (rs2228000)	Val/Val	72 (20.60)	181 (45.25)	1			
	Val/Arg	56 (16.00)	88 (22.00)	1.59 (1.03-2.46)	*0.03*	1.56 (1.009-2.43)	0.04
	Arg/Arg	222 (63.40)	131 (32.75)	**4.26 (3.007-6.03)**	***<0.0001****	**4.17 (2.93-5.93)**	***<0.0001****
	Val/Arg+Arg/Arg	278 (79.40)	219 (54.75)	**5.87 (4.14-8.31)**	***<0.0001****	**3.22 (2.32-4.46)**	***<0.0001****
XPC Lys939Gln Cd939 Exon15 (rs2228001)	Lys/Lys	173 (49.40)	198 (49.50)	1		1	
	Lys/Gln	141 (40.30)	175 (43.75)	0.92 (0.68-1.24)	0.59	0.87 (0.63-1.206)	0.41
	Gln/Gln	36 (10.30)	27 (6.75)	1.52 (0.89-2.61)	0.12	1.42 (0.80-2.52)	0.22
	Lys/Gln+ Gln/Gln	177 (50.60)	202 (50.50)	1.00 (0.75-1.33)	0.98	1.003 (0.74-1.35)	0.98
XPC -371promoter G>A (rs3731055)	G/G	295 (84.30)	331 (82.75)	1		1	
	G/A	28 (8.00)	17 (4.25)	1.84 (0.99-3.44)	0.05	1.79 (0.93-3.46	0.07
	A/A	27 (7.70)	52 (13.00)	0.58 (0.35-0.95)	0.03	0.62 (0.37-1.04)	0.07
	G/A+ A/A	55 (15.70)	69 (17.25)	0.89 (0.60-1.31)	0.57	0.82 (0.55-1.24)	0.35
XPG His1104 Asp codon1104 Ex-15 (rs17655)	His/His	203 (58.00)	238 (59.50)	1		1	
	His/Asp	125 (35.70)	143 (35.75)	1.02 (0.75-1.38)	0.89	0.99 (0.72-1.38)	0.99
	Asp/Asp	22 (6.30)	19 (4.4.75)	1.28 (0.68-2.42)	0.43	1.46 (0.73-2.93)	0.28
	His/Asp+ Asp/Asp	147 (42.00)	162 (40.50)	1.05 (0.78-1.40)	0.72	1.05 (0.77-1.42)	0.72

*: Indicates significant Odds Ratio ($p<0.0001$) *p* value determined based on $\chi 2$

(B) Analysis of the *His1104 Asp* polymorphism in the XPG gene

To study the correlation between Asp 1104 His (C> G) polymorphism in the exon 15 of XPG gene, 350 cases and 400 controls were genotyped. The amplification of XPG codon 1104 resulted in 271bp. The PCR amplified products upon treatment with NlaIII yielded wild-type (3507CC) allele of 271bp fragment and the polymorphic GG allele produces 227 and 44bp fragments. The frequency of XPG3507CC homozygote was 58 % in cases and 59.5 % in controls whereas the frequency of *3507GG* allele was significantly lower in the cases (6.3 %) and the controls (4.75 %). The frequency of *3507CG* heterozygotes was 35.7 % in cases and 35.75 % in controls (Table-2). Women carrying the *XPG* Asp1104Asp (GG) genotype had no association with risk for CC (OR = 1.28, 95% CI = 0.68–2.42, *p*=0.43).

Table 3: Stratification Analysis of the Demographic Factors Including Age, Tobacco Smoking, Age at First Delivery and Distribution of Genotypes of the XPC and XPG genes in Patients with CC and Control Group from Population of Maharashtra

		Demographic Factors							
Gene	**Genotype**	**Age (Cases/Control)**		**Tobacco status (Cases/Control)**		**Age @ 1st pregnancy (Cases/Control)**			
		⩽ 50 N=216/286	> 50 N=134/114	Users N=189/113	Non-Users N=161/287	15-20 N=277/183	21-25 N=72/178	26-30 N=0/34	31-35 N=1/5
XPC Val499Arg Cd499 Exon8 (rs2228000)	Val/Val	48/130	24/51	35/53	37/128	59/83	13/83	0/12	0/3
	Val/Arg+ Arg/Arg	168/156	110/63	154/60	124/159	219/100	59/95	0/22	1/2
	OR (95% CI)	2.91 (1.96-4.33)	3.71 (2.08-6.59)	3.88 (2.30-6.54)	2.69 (1.74-4.16)	3.08 (2.04-4.63)	3.96 (2.03-7.73	0.55 (0.01-29.47)	4.20 (0.11-151.0)
	P value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0001**	0.77	0.43
XPC Lys939Gln Cd939 Exon15 (rs2228001)	Lys/Lys	107/145	66/53	96/65	77/133	133/92	39/82	0/20	1/4
	Lys/Gln+ Gln/Gln	109/141	68/61	93/48	84/154	144/91	33/96	0/14	0/1
	OR (95% CI)	1.04 (0.73-1.49)	0.89 (0.54-1.47	1.06 (0.65-1.73)	0.94 (0.64-1.38)	1.09 (0.75-1.59)	0.72 (0.41-1.25)	1.41 (0.02-75.41)	1.22 (0.03-48.01)
	P value	0.79	0.66	0.78	0.76	0.63	0.24	0.86	0.91
XPC -371promoter G>A (rs3731055)	G/G	184/232	111/99	160/61	135/270	233/153	61/143	0/30	1/5
	G/A+ A/A	32/54	23/15	29/52	26/17	44/30	11/35	0/4	0/0
	OR (95% CI)	0.74 (0.46-1.20)	1.36 (0.67-2.76)	0.21 (0.12-0.36)	3.05 (1.60-5.83)	0.96 (0.58-1.59)	0.73 (0.35-1.54)	6.77 (0.11-386.3)	3.66 (0.049-274.5)
	P value	0.23	0.38	<0.0001	0.0007	0.88	0.41	0.35	0.55
XPG His1104Asp codon1104 Ex-15 (rs17655)	His/His	126/170	77/67	106/71	97/166	164/119	38/103	0/16	1/2
	His/Asp+ Asp/Asp	90/116	57/47	83/42	64/121	113/64	34/75	0/18	0/3
	OR (95% CI)	1.04 (0.73-1.49)	1.05 (0.63-1.75)	1.32 (0.82-2.13)	0.90 (0.61-1.34)	1.28 (0.87-1.88)	1.22 (0.70-2.13)	0.89 (0.01-47.52)	0.23 (0.006-8.61)
	P value	0.80	0.83	0.24	0.61	0.20	0.46	0.95	0.43

C) Effect of age of cancer occurrence, tobacco status and age at Ist pregnancy on the association of XPC and XPG with cervical cancer risk

The genotype distributions of the selected XPC and XPG gene polymorphisms in cases and controls and their associations with CC risk are summarized in Table 3. Variables including age, smoking, drinking, and age at first pregnancy were adjusted for in the subsequent multivariate logistic regression analyses. The logistic regression analysis showed that none of the SNPs other than rs2228000 was associated with CC risk in homozygotes or heterozygotes after being adjusted for age, tobacco smoking status and the earlier age at first pregnancy. When we compared CC genotype of rs222800 with CT/TT genotypes showed increased association with CC risk after adjustment with age (OR =2.91, 95% CI =1.96–4.33, p<0.0001), Tobacco status (OR =3.88, 95% CI =2.30–6.54, p<0.0001) and early age at first pregnancy (OR =3.08, 95% CI =2.04–4.63, p<0.0001). To examine the association of the polymorphisms with the median age at the time of CC diagnosis, we stratified the patients according to the age (Table 1) as ⩽ 50 (n= 216) or >50 (n = 134) years and compared them with age-matched controls. The analyses showed association of GG allele of XPC at codon 499 of exon 8 (OR= 2.91; 95% CI= (1.96-4.33, p= <0.0001) with cervical cancer risk in women at or below 50 years of age (Table 3). However, when we compared XPC codon 3939 and -371 promoter of XPC in relation with age bellow 50 years did not show any association with CC development. Similarly, variants in SNP rs17655 of XPG at codon 1104 did not show increased association (OR=1.04; 95% CI= (0.73-1.49), p= 0.80) with CC. When we compared age for the first pregnancy, only XPC499 variant (OR=3.08; 95% CI= (2.04-4.63), p <0.0001) showed significant risk of CC in patients with delivery age group below 15-20 years higher risk (Table-3) than in other polymorphisms including XPCLys939Gln, XPC-371 promoter and XPGHis1104Asp.

Discussion:

A hospital based case-control study was performed to investigate the association between three potentially functional SNPs in the XPC and one SNP of XPG gene and the risk of CC in a rural population of south-western Maharashtra. To assess the association of XPC and XPG variants and risk of CC, crude and adjusted ORs and their 95% CIs were calculated using both homozygous genotypes or combined with their respective heterozygous genotypes. The results showed that none of the polymorphisms in the *XPC or XPG* gene had a significant effect on the risk of developing CC except SNP rs2228000 of the exon 8 in XPC gene. Furthermore, the results also indicate that the XPC Val499Arg polymorphism was associated with increased risk of CC among subgroups of early pregnancy subjects and with tobacco smokers. This is the first report that deals with the XPC variation Val499Arg which significantly contributes to CC susceptibility in females and suggests the importance of XPC in cervical carcinogenesis.

We did not find evidence of significant association between XPCLys939Gln or XPG Asp1104His with CC risk. In the stratified analysis, age, smoking status and age of the pregnancy had no

effect on the association between the rs2228001 A>C, rs3731055 G>A polymorphism of XPC, rs17655 G>C of XPG and risk of CC except rs2228000 C>T polymorphism of XPC. The polymorphism in XPC and XPG genes has been extensively investigated for its associations with cancer risk and the results were inconclusive in different types of cancer or different populations. XPC polymorphisms and their estimated haplotypes are associated with lung cancer [15] and gallbladder cancer risk [16]. But, there are no evidences of significant association between XPC polymorphisms and the risk of colorectal [17] and gastric cancer [18]. Similarly, several reports explored the correlation between the *XPG* Asp1104Asp polymorphisms and risk of multiple cancer including lung cancer and oral squamous cell carcinomas [19-20]. Studies also indicated that polymorphisms in the XPG gene are associated with the development of breast, lung, prostate, colorectal cancer and osteosarcoma [8, 17, 21-24]. Few studies indicated that XPG rs17655 G>C polymorphisms do not show any association with the risk of head and neck cancer [25-26]. Similarly polymorphisms in XPC and XPG are reported to be associated with risk of different cancers including lung, bladder and prostate cancer in Indian population [27-29].

The non-availability of association studies related to the role of XPC and XPG in cervical cancer allowed us to assess the risk posed by variant alleles of XPC or XPG and to speculate the influence of functional variations in individual's susceptibility to cervical cancer. Therefore, we determined the relationship between the development of CC and genetic polymorphisms in XPC & XPG genes from a pool of unexplored rural Maharashtrian population and we found contribution of XPC codon 499 of exon 8 XPG to the development of cervical cancer.

Conclusion:

In conclusion, to our knowledge this study is the first one to show that XPC Val499Arg polymorphism at codon 499 of exon 8 associated with susceptibility to cervical cancer in women of rural population of south-western Maharashtra.

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