



Polymorphisms in XPC gene and risk for prostate cancer

Rahma Said^{1,4} · Karim Bougateg² · Nouha Setti Boubaker¹ · Rim Jenni¹ · Amine Derouiche³ · Mohamed Chebil³ · Slah Ouerhani¹

Received: 8 November 2018 / Accepted: 10 December 2018 / Published online: 14 December 2018
© Springer Nature B.V. 2018

Abstract

Single nucleotide polymorphisms (SNP) in repair gene DNA such as XPC gene can reduce the DNA repair capacity (DRC). Reduced DRC induce genetic instability and may increase the susceptibility to prostate cancer (PC). We conducted a case-controls study to examine the relationship between XPC Lys939Gln and XPC-PAT polymorphisms and the risk for prostate cancer in Tunisian population. We have also correlated molecular results with clinical parameters (Gleason score and TNM status) and lifestyle factors (tobacco status, alcohol consumption, and exposition to professional risk factors) of prostate cancer patients. We have found that the XPC Lys939Gln polymorphism was not associated with a risk of prostate cancer. However the XPC PAT I/I genotype was found to be associated with 3.83-fold increased risk of prostate cancer compared to controls ($p = 0.00006$; OR 3.83; 95% CI (1.83–8.05)). The test of linkage disequilibrium showed that XPC-PAT polymorphism is in linkage disequilibrium with XPC Lys939Gln variants. The combined analysis of XPC Lys939Gln and XPC-PAT variants showed that patients who inherited (Lys/Gln + PAT D/D) genotypes were protected against prostate cancer development compared to controls. In the other hand, no significant association has been found between XPC polymorphisms and clinical parameters or between XPC polymorphisms and lifestyle factors.

Keywords Polymorphism · Prostate cancer · Xeroderma pigmentosum complementary group C · Tunisia

✉ Slah Ouerhani
slah_mekni@yahoo.fr

Rahma Said
ramasaid649@gmail.com

Karim Bougateg
karimhamhama@yahoo.fr

Nouha Setti Boubaker
nouha.setti@hotmail.fr

Rim Jenni
rim.jenni19@gmail.com

Amine Derouiche
amine_derouiche@yahoo.fr

Mohamed Chebil
mohamed.chebil@yahoo.fr

¹ Laboratory of Protein Engineering and Bio-active Molecules, National Institute of Applied Science and Technology - University of Carthage, Tunis, Tunisia

² Laboratory of Genetics, Immunology and Human Pathology, Faculty of Sciences of Tunis, Tunis, Tunisia

³ Urology Department, Charles Nicolle Hospital, Tunis, Tunisia

⁴ Faculty of Sciences of Bizerte, University of Carthage, Carthage, Tunisia

Abbreviations

SNP	Single nucleotide polymorphisms
DRC	DNA repair capacity
PC	Prostate cancer
PSA	Prostate-specific antigen
NER	Nucleotide excision repair
BER	Base excision repair
MMR	Mismatch repair
DSBR	Double-strand break repair
TCR	Transcription-coupled repair
XPC	Xeroderma pigmentosum complementary group C
DRE	Digital rectal examination
EDTA	Ethylene diamine tetra-acetic acid
PCR	Polymerase chain reaction
PCR-RFLP	Restriction Fragment Length polymorphism
ORs	Odds ratios
CI	Confidence intervals

Introduction

Prostate cancer (PC) is the most frequently diagnosed malignancy among men in western countries and the sixth leading cause of cancer-specific death worldwide [1]. The International Agency for Research on Cancer reported that PC accounted for 15% of total new cancer cases in 2012. In Tunisia, PC is considered as the third most diagnosed cancer in men with the incidence of $14.1/10^5$ person-years in 2007 [2]. External exposures, including lifestyle factors and genetic predisposition, were the most risk factors for prostate cancer [3–5]. Prostate-specific antigen (PSA) testing for PC has been in common practice for more than 20 years. Prognosis of prostate cancer depends on the risk stratification D'Amico classification [6]. This method is based on three factors: prostate specific antigen (PSA), Gleason score and clinical stage [6]. Deficient DNA repair capacity is known to be cancer predisposing factor. Indeed the presence of some Single nucleotide polymorphisms (SNP) in repair gene DNA can change the function of repair enzyme and corrupt their level of transcription or translation. These modifications can reduce the DNA repair capacity (DRC) and induce genetic instability, in turn, activate the susceptibility to carcinogenesis. There are five major important DNA-repair pathways consisting of more than 130 genes: nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), and double-strand break repair (DSBR) and transcription-coupled repair (TCR) [7]. Among these pathways, NER is the most important DNA repair mechanism responsible for various types of DNA damage consisting of oxidative DNA damage, bulky adducts cross-links, alkylating damage and thymidine dimmers [7].

Xeroderma pigmentosum complementary group C (XPC) is an important component of the NER pathway [8]. This gene is localized on chromosome 3p25 and hosts 16 exons (82–882 bp) and 15 introns (0.08–5.4 kb) encodes for a 940 amino acid protein that has a major role in the repair of complex protein formations [8]. The functional DNA-binding domains interact with HR23B to form a complex that recognizes and binds to the sites of DNA damage. Many researchers have confirmed the role of XPC in the regulation of the cell cycle for DNA damage response and oxidative damage on cells [9]. More than one hundred SNPs in the coding regions of XPC have been reported. The most common and studied SNPs are XPC Lys939Gln and XPC poly (AT) [10]. XPC Lys939Gln is a single nucleotide polymorphism (XPC rs2228001 A 33512> C) consisted in the modification of the nucleotide A to C leading to modification from Lysin to Glutamine proteins at 939 positions of the DNA repair XPC gene. Single nucleotide polymorphisms of XPC Lys939Gln can

reduce recognition and repair of DNA damage, protein expression, thus leading to more somatic DNA mutations or alteration to occur [11]. XPC-PAT is an insertion/deletion polymorphisms of XPC gene consisting of an insertion of 83 bases of A to T [poly(AT)] and deletion of 5 bases (GTAAC) at positions 1457 to 1461 in intron 9 [12]. This polymorphism can inhibit DRC and increase the risk for tumorigenesis [13]. Although the XPC Lys939 Gln and XPC-PAT polymorphisms have been implicated with altered susceptibility in a number of cancers [14, 15]; studies focusing on their relationship with the risk of prostate cancer have produced the same results. Indeed, Hirata et al. suggested that the 939 Gln mutant allele was significantly higher in PC cases in the Japanese population [16] and Wu et al. have not found a significant relationship between XPC Lys939Gln variant and PC occurrence [17]. With considering the XPC-PAT polymorphism, some studies have reported that the mutant genotype (PAT I/I) is associated with increasing PC risk in different populations such as Indian, Chinese, Japanese, Iranian American and Caucasian [18, 19].

In view of that, this work addresses the relationship between XPC Lys939Gln and XPC-PAT polymorphisms and the predisposition to prostate cancer in a case-control study of a previously unstudied Tunisian cohort aiming at clarifying whether genetic variations in XPC represent risk factors for the development of prostate cancer in Tunisia. We have also analyzed the correlation between XPC polymorphisms and tumor characteristics and/or clinical outcome.

Materials and methods

Subjects

This project was approved by a local ethical committee. Informed consent was obtained from all individual participants included in the study. A total of 110 consecutive PC patients were included in this study. All patients had previously undergone prostate biopsy for detection of PC at the Department of Urology at the Charles Nicole Hospital of Tunis; Tunisia. The typical indications for prostate biopsy were: total PSA level > 4.0 ng/ml and abnormal digital rectal examination (DRE) for the prostate nodule and then they were confirmed by the result of the pathology report. The clinical and epidemiological parameters of PC cases were summarized in Table 1. Clinical Characteristics of prostate cancer were obtained from medical records, enrolling PSA level, Gleason pathological score, Tumor stage, and TNM status.

The controls were 266 men matched to PC patients for age and geographic origin. They included 145 individuals

Table 1 Clinical and epidemiological characteristics of prostate cancer patients

Clinical and epidemiological parameters	Prostate cancer	Controls
Samples sizes	110	266
Age at diagnosis (years)	71.79 ± 11.27	68.99 ± 8.51
PSA mean (ng/ml)	111.41	2.225 ± 1.5
Gleason score		
Low score (Gleason score < 7)	32 (29.10%)	–
Intermediate score (Gleason score = 7)	36 (32.72%)	–
High score (Gleason score > 7)	42 (38.18%)	–
Tumor stage		
T1	22 (20.00%)	–
T2	17 (15.46%)	–
T3	34 (30.90%)	–
T4	22 (20.00%)	–
Not available information	15 (13.64%)	–
TNM classification		
T1-T2N0M0	30 (27.27%)	–
T3-T4N0M0	25 (22.73%)	–
TNxM+	40 (36.36%)	–
Not available informations	15 (13.64%)	–
Smoking status		
Smokers	82 (74.55%)	214 (80.45%)
Non smokers	28 (25.45%)	52 (19.54%)
Number of pack/years		
< 20 PY	22 (26.83%)	94 (43.92%)
≥ 20 PY	60 (73.17%)	120 (56.08%)
Alcohol consumption		
Drinkers	54 (49.09%)	123 (46.24%)
No drinkers	56 (50.91%)	143 (53.76%)
Exposure to professional risk factors		
Not exposed	52 (47.28%)	120 (44.11%)
Exposed	58 (52.72%)	146 (54.89%)

TNM tumor nodes metastasis, PY packet year

with benign prostatic hyperplasia (BPH) and normal PSA levels and 121 healthy individuals with unknown BPH status. BPH samples were identified by their normal pathological reports of transrectal prostate biopsy in the case when PSA was > 4.0 ng/ml. The anatomopathological reviewed the tumor characteristics and screened for the absence of any signs of malignancy in the Formalin Fixed Paraffin Embedded (FFPE) tissues of BPH controls and the follow up of PSA for BPH samples after treatment is < 4 ng/ml. Healthy individuals included in this study are volunteers enrolled in the external consultation and they have normal digital rectal examination (DRE), serum PSA < 0.2 ng/ml and devoid from any forms of cancer.

Molecular analysis

Peripheral blood samples were collected from all subjects into tubes with ethylene diamine tetra-acetic acid (EDTA) at pH 8. Genomic DNA was extracted by a conventional phenol/chloroform protocol [20]. The quantity and quality of extracted DNA were estimated by a Nanodrop.

The XPC–PAT polymorphism was genotyped by Polymerase Chain Reaction (PCR) followed by electrophoresis on 1% agarose gel. The used primers and fragments sizes were summarized in Table 2. The PCR reaction was carried out in a total volume of 25 µl containing 50 ng of genomic DNA, 1 X of DNA polymerase Taq buffer, 2.5 mM of MgCl₂, 0.2 mM of dNTP, 0.32 µM of each primer and 1 U of Taq DNA polymerase (Invitrogen™). Thermal cycling conditions were: an initial step of 95 °C for 10 min followed by 35 cycles of denaturing step at 95 °C for 45 s, 63 °C for 45 s and 72 °C for 45 s, followed by a final elongation step at 72 °C for 10 min. The PCR product was resolved by agarose gel electrophoresis (1%) and visualized by UV radiation after ethidium bromide staining. The homozygous wild genotype (PAT D/D) has resulted in a 266-bp amplification. However, the homozygous mutant genotype (PAT I/I) was characterized by the presence of only a 344-bp fragment.

The XPC Lys939Gln was genotyped by PCR-RFLP (restriction fragment length polymorphism). The used PCR primers for XPC Lys939Gln polymorphism were summarized in Table 2. The volume of PCR reaction was carried out in a final volume of 25 µl containing 50 ng of genomic DNA, 0.24 µM of each primer, 1X of Taq DNA polymerase buffer, 2.5 mM of MgCl₂, 0.20 mM of dNTP, and 1U of Taq DNA polymerase (Invitrogen™). After initial denaturation at 95 °C for 5 min, PCR reactions were carried out for 35 cycles at 95 °C for 45 s, 64 °C for 45 s and 72 °C for 45 s, followed by a final elongation step at 72 °C for 10 min. The PCR product was digested by 10U of a PvuII enzyme (New England Biolabs) for 4 h at 37 °C and analyzed by agarose gel electrophoresis at 1.5%. The wild genotype XPC Lys/Lys was characterized by the presence of only one fragment of 244 pb. However, the homozygous and heterozygous genotypes (Gln/Gln) and (Lys/Gln) were respectively marked by the presence of two fragments of 189 and 55 pb and three fragments of 244.189 and 55 pb.

Statistical analysis

The Hardy Weinberg equilibrium test as calculated by the software package Arlequin (version 3.01) [21]. The difference of genotypes frequencies between cases and controls were determined by the χ^2 test. In addition odds ratios (ORs) and their 95% Confidence Intervals (95% CI) were calculated as a measure of the association of the polymorphic

Table 2 Primers used for XPC Lys939Gln and XPC-PAT genotyping

Studied polymorphism	Gene (exon/intron)	Primer sequence	Annealing temperature (°C)	Fragment sizes
rs2228001 A > C (Lys939Gln)	XPC_Exon 15	F:5'-GATGCA GGAGGTGGA CTCTCT-3' R:5'-GTAGTG GGGCAGCAG CAA CT-3'	64	244pb
XPC-PAT	XPC_Intron 9	F:5'-TAGCAC CCAGCAGTC AAAG-3' R:5'-TGTGAA TGTGCTTAA TGCTG-3'	63	266pb ^a /344 pb ^b

^aHomozygous wild genotype^bHomozygous mutant genotype**Table 3** Hardy Weinberg equilibrium for XPC Lys939Gln and XPC-PAT polymorphisms

Variants	Groups					
	Controls (N = 266)			Prostate cancer (N = 110)		
	Obs. Het	Exp. Het	p value	Obs. Het	Exp. Het	p value
XPC Lys939Gln	0.5939	0.5487	0.7321	0.50000	0.48032	0.69155
XPC PAT	0.3609	0.3812	0.4189	0.38182	0.48219	0.03357

Obs. Het observed heterozygous genotype, *Exp. Het* expected heterozygous genotype**Table 4** Comparison of genotypes distribution of XPC Lys939Gln and XPC-PAT in controls and prostate cancer (PC) from Tunisian population

Genotypes	Controls N = 266	Prostate cancer N = 110	Controls group vs prostate cancer patients		
			p value	OR	95% CI
XPC Lys939Gln					
Lys/Lys	82 (30.83%)	39 (35.45%)	–	1*	–
LyLys/Gln	158 (59.39%)	55 (50.00%)	0.21	0.73	0.44–1.23
Gln/Gln	26 (9.78%)	16 (14.55%)	0.48	1.29	0.58–2.85
Lys/Gln + Gln/Gln	184 (69.17%)	71 (64.55%)	0.38	0.81	0.49–1.33
XPC*Lys	322 (0.605)	133 (0.605)	–	1**	–
XPC*Gln	210 (0.395)	87 (0.395)	0.98	1.00	0.72–1.40
XPC-PAT					
D/D	150 (56.39%)	45 (40.91%)	–	1*	–
D/I	96 (36.09%)	42 (38.18%)	0.13	1.46	0.87–2.46
I/I	20 (7.52%)	23 (20.91%)	0.00006	3.83	1.83–8.05
D/I + I/I	116 (43.61%)	65 (59.09%)	0.006	1.87	1.16–3.01
XPC*D	396 (0.744)	132 (0.600)	–	1**	–
XPC*I	136 (0.256)	88 (0.400)	0.00008	1.94	1.37–2.74

OR odds ratio, 95% CI confidence interval

1* and 1** reference groups

Table 5 Combined effect of XPC Lys939Gln and XPC-PAT polymorphisms in prostate cancer susceptibility

Genotypes	Controls N = 266	Prostate cancer N = 110	Control group VS prostate cancer patients		
			p value	OR	95% CI
XPC Lys-939Gln + XPC-PAT					
Lys/Lys + D/D	57 (21.43%)	32 (29.09%)	–	1*	
Lys/Lys + D/I	24 (9.02%)	6 (5.45%)	0.105	0.45	0.15–1.31
Lys/Lys + I/I	1 (0.37%)	1 (0.90%)	0.68	1.78	0–67.91
Lys/Gln + D/D	81 (30.45%)	12 (10.90%)	0.0002	0.26	0.12–0.59
Lys/Gln + D/I	68 (25.57%)	35 (31.81%)	0.77	0.92	0.48–1.74
Lys/Gln + I/I	9 (3.39%)	8 (7.27%)	0.38	1.58	0.49–5.06
Gln/Gln + D/D	12 (4.51%)	1 (0.90%)	0.08**	0.15	0.01–1.19
Gln/Gln + D/I	4 (1.51%)	1 (0.90%)	0.46	0.45	0.02–4.56
Gln/Gln + I/I	10 (3.75%)	14 (12.72%)	0.08**	2.49	0.91–6.92

OR odds ratio; 95% CI confidence interval
1* reference group; ** corrected p-value

sites with prostate cancer risk. A p-value was considered significant at < 0.05.

Results

Hardy Weinberg equilibrium for XPC Lys939Gln and XPC-PAT polymorphisms for control subjects and prostate cancer patients are shown in Table 3. All samples were found to be in Hardy Weinberg equilibrium (p > 0.05) except for prostate cancer patients among whom the genotypic distribution for XPC-PAT polymorphism showed a statistical difference from Hardy Weinberg expectations (p = 0.03357). The frequencies of XPC*C allele (XPC 939*Gln) were estimated at 0.395 in both control group and prostate cancer patients. The frequencies of XPC*I allele were estimated at 0.256 and 0.400 in respectively control group and prostate cancer patients. The percentages of XPC PAT I/I genotypes in control group and prostate cancer patients were respectively estimated at 7.52% and 20.91%. The comparison of XPC Lys939Gln genotypes frequencies between control group and prostate cancer patients has not reported a significant difference (Table 4). However the XPC PAT I/I genotype has been

Table 6 Comparison of genotypes distribution of XPC Lys939Gln and XPC- PAT in prostate cancer patients according to tobacco status and alcohol consumption

Genotypes	Tobacco status			Alcohol consumption			Non smokers versus moderate smokers		Non smokers versus highly drinkers		No drinkers versus drinkers	
	Non smokers	Moderate < 20PY	Highly ≥ 20PY	No- drinkers	Drinkers	OR (95% CI)		OR (95% CI)		OR (95% CI)		
						*	**	*	**	***	***	
XPC Lys939Gln												
Lys/Lys	10	5	24	19	20	–	–	–	–	–	–	1*
Lys/Gln	12	16	27	28	27	0.13	0.89	1*	–	0.83	–	–
Gln/Gln	6	1	9	9	7	0.35	0.46	–	–	0.61	–	–
XPC-PAT												
D/D	9	8	28	22	23	–	–	–	–	–	–	1*
D/I	14	13	15	23	19	0.94	0.07****	1*	–	0.58	–	–
I/I	5	1	17	11	12	0.18	0.88	–	–	0.93	–	–
XPC Lys939Gln/ XPC-PAT												
Lys/Lys + D/D	7	3	22	15	17	–	–	–	–	–	–	1*
Gln/Gln + I/I	5	1	8	8	6	0.55	0.34	–	–	–	–	–

OR odds ratio, 95% CI confidence interval, PY packet year
*, **, ***, ****-p-value; 1* reference group; ****-corrected p-value

found to be associated with 3.83 increased risk of prostate cancer compared to control group ($p = 0.00006$; OR 3.83; 95% CI 1.83–8.05). The test of linkage disequilibrium showed that XPC-PAT polymorphism is in linkage disequilibrium with XPC Lys939Gln variants. The combined analysis of XPC Lys939Gln and XPC-PAT variants showed that patients who inherited Lys/Gln + PAT D/D genotypes are protected against prostate cancer development compared to controls (Table 5).

The comparison between PC patients according to tobacco status and XPC Lys939Gln or XPC PAT polymorphisms doesn't report any significant association (Table 6). This result suggests that there isn't an additive effect between tobacco and the studied polymorphisms. The same result was obtained when we compare the distribution of XPC Lys939Gln or XPC-PAT polymorphism between drinkers and non-drinkers of alcohol (Table 6). In the other hand, the correlations between XPC gene polymorphisms and clinical parameters of prostate cancer patients (Gleason Score and TNM) don't report any significant association (Tables 7, 8).

Discussion

In this population based case-control study, we investigated the effect of environmental risk factor and gene repair polymorphisms on prostate cancer (PC) development and their association with clinical and epidemiological parameters.

The allele frequency for XPC*C (XPC*Gln) in Tunisian control group is estimated at 0.395. This frequency is lower to which reported for the Caucasian and African populations [18, 22]. The comparison of PC and control group according

to XPC Lys939Gln polymorphism has not reported a significant difference. This result confirms many recent meta-analyses. Indeed, in the meta-analysis of Wu et al., authors have found that the XPC Lys939Gln polymorphism was not associated with PC susceptibility [17]. In this study, authors have also reported that in the subgroup analysis by ethnicity, no significant association was found in three ethnic groups (Asian, Caucasian, and African). Moreover, in the meta-analysis of He et al. authors have found an increased cancer risk associated with this polymorphism in the homozygous genetic model for Asian populations, but not for other ethnic groups [7]. Conversely, Hirata et al. have found that the frequency of 939Gln variant at XPC Lys939Gln was significantly lower in PC cases and was associated with a protective effect (OR 0.39, $p = 0.016$) [16].

The comparison of PC cases with controls according to XPC-PAT polymorphism, suggests that individuals inheriting XPC I/I genotype were at significantly increased risk of PC malignancy. This result confirms others reported studies and was explained by the fact that the homozygous variant genotype of the PAT polymorphism (I/I) exhibited lower DRC as compared to wild-type carriers (D/D) [16, 23]. To the best of our knowledge, it is the first study in which we report a high association between prostate cancer and XPC I/I genotype (OR 3.83). Indeed, all of the previously reported studies interested in the analysis of the association between XPC-PAT polymorphism and prostate cancer suggest a moderate risk association which doesn't exceed 2.5-fold increased risk [24]. The observed high-risk association between XPC I/I genotype and prostate cancer in Tunisian population in comparison to other populations could be associated to the difference in ethnicity and may be also explained by the additive effect between the inheritance of

Table 7 Combined analysis of XPC gene polymorphisms and Gleason score of PC patients

	Low Gleason score < 7	Intermediate Gleason score = 7	High Gleason score > 7	Between low and intermediate Gleason score		Between low and high Gleason score	
	N	N	N	**	OR (95% CI)	**	OR (95% CI)
XPC Lys939Gln							
Lys/Lys	10	14	15	–	1*	–	1*
Lys/Gln	15	16	24	0.61	0.76 (0.23–2.55)	0.90	1.07 (0.34–3.37)
Gln/Gln	7	6	3	0.47	0.61 (0.13–2.91)	0.146	0.29 (0.04–1.70)
XPC-PAT							
D/D	13	13	19	–	1*	–	1*-
D/I	11	16	15	0.49	1.45 (0.43–4.98)	0.89	0.93 (0.29–3.04)
I/I	8	7	8	0.83	0.88 (0.20–3.75)	0.53	0.68 (0.17–2.69)
XPC Lys939Gln + XPCPAT							
Lys/Lys + D/D	9	11	12	–	1*	–	1*
Gln/Gln + I/I	7	5	2	0.46	0.58 (0.11–3.10)	0.08***	0.21 (0.02–1.61)

OR odds ratio, 95% CI confidence interval

p-value; 1*: Reference group; *Corrected p-value

Table 8 Logistic regression: effect of tobacco and XPC polymorphisms on PC tumors stages

T ^a	B	Std. error	df	Sig.	Exp(B) = OR	95% confidence interval for exp(B)	
						Lower bound	Upper bound
T2							
Intercept	− 15.872	1.138	1	0.000			
[XPClys939Gln = Gln/Gln]	− 18.096	5510.253	1	0.997	1.384E-8	0.000	0
[XPClys939Gln = Lys/gln]	− 0.064	0.859	1	0.940	0.938	0.174	5.053
[XPClys939Gln = Lys/lys]	0 ^b		0				
[XPCPAT = D/D]	16.625	0.909	1	.000	16593626.569	2795301.292	98504030.131
[XPCPAT = D/I]	16.237	0.000	1		11267481.664	11267481.664	11267481.664
[XPCPAT = I/I]	0 ^b		0				
[Tobacco status = smokers]	− 0.510	0.866	1	0.556	0.600	0.110	3.278
[Tobacco status = non smokers]	0 ^b		0				
T3							
Intercept	2.961	1.492	1	0.047			
[XPClys939Gln = Gln/Gln]	− 2.781	1.373	1	0.043	0.062	0.004	0.915
[XPClys939Gln = Lys/gln]	− 1.156	0.814	1	0.156	0.315	0.064	1.552
[XPClys939Gln = Lys/lys]	0 ^b		0				
[XPCPAT = D/D]	− 1.703	1.291	1	0.187	0.182	0.015	2.285
[XPCPAT = D/I]	− 0.958	1.251	1	0.443	0.384	0.033	4.449
[XPCPAT = I/I]	0 ^b		0				
[Tobacco status = smokers]	− 0.554	0.704	1	0.431	0.575	0.145	2.283
[Tobacco status = non smokers]	0 ^b		0				
T4							
Intercept	1.271	1.702	1	0.455			
[XPClys939Gln = Gln/Gln]	− 3.579	1.719	1	0.037	0.028	0.001	0.811
[XPClys939Gln = Lys/gln]	− 0.059	0.875	1	0.946	0.943	0.170	5.238
[XPClys939Gln = Lys/lys]	0 ^b		0				
[XPCPAT = D/D]	− 2.082	1.357	1	0.125	0.125	0.009	1.782
[XPCPAT = D/I]	− 1.290	1.293	1	0.318	0.275	0.022	3.468
[GXPCPAT = I/I]	0 ^b		0				
[Tobacco status = smokers]	0.745	0.974	1	0.444	2.106	0.313	14.197
[Tobacco status = non smokers]	0 ^b		0				

Logistic regression: number of observation = 95, Chi square: 27.391, $p = 0.072$, Pseudo R-square = 0.250, Log likelihood = 74.08

^aThe reference category is PC with tumour stage T1

^bThis parameter is set to zero because it is redundant

XPC I/I genotype, tobacco and professional risk factors. Indeed 74.75% (82/110) of PC patients were smokers and 54.54% of them (60/110) were highly smokers. Moreover it has been found that more than 52% of PC patients are exposed to professional risk factors. Among the professional risk factors we cited aromatic amines (benzidine, 4-aminobiphenyl, 2-naphthylamine, 4-chloro-o-toluidine), chlorinated hydrocarbon or polycyclic aromatic hydrocarbons, or pesticides use mainly in industrial areas processing paint, metal, dye, petroleum derivatives or agriculture fields. These observations highlight the imperative need to enlarge the predispositions studies in the Tunisian populations in this concern in order to raise the awareness about the use

and composition of chemical products. Our result is supported by the study of However, Liu et al. Which suggest that XPC-PAT polymorphisms may contribute to the risk of developing PC and have found an elevated risk of PC associated with a gene-environment interaction [8].

In accordance with previous reports, we detected linkage disequilibrium between XPC Lys939Gln and XPC PAT polymorphisms [25]. We have found that the inheritance of the (Lys/Gln + PAT D/D) haplotype had a protective effect. This result was explained by the presence of the wild allele PAT*D (dominant allele) which modulate the effect of the XPC* 939Lys or *939Gln allele. However, we have not found an additive effect between XPC Gln/Gln and I/I

genotypes. This result is in contradiction with previous studies which have found that the mutant diplotype (Gln/I) could be considered as an aggravating marker for prostate cancer [25, 26]. Moreover we have not found a significant association between Lys/Lys + I/I or Lys/Gln + I/I and PC risk, although the inheritance of the risk genotype PAT I/I. These results could be explained by the low number of subjects with Lys/Lys + I/I genotype (only 0.5% of patients and controls) and also by the interaction among the the XPC polymorphisms. Indeed it has been reported that the obtained results for the XPC haplotype could be explained by contradictory results frequently found in studies based on individual-SNP analyzes. Indeed if the interactions between individual-SNP contribute to tumor risk, then the haplotype/diploypes constructed by these polymorphisms may exert different effects on tumorigenesis in comparison to individual SNPs [27, 28]. Moreover the interactions between polymorphisms, environmental factors and host characteristics of PC patients might contribute to the discrepancies.

The combined analysis of XPC gene polymorphisms and Gleason score of PC patients don't report any significant result which confirms others previously reported studies [11, 29]. Conversely, Mandal et al. reported that XPC-PAT polymorphism is associated with high Gleason score in Indian population and explained this association by the fact that the interactions among genetic polymorphisms in NER pathway genes may affect the DNA damage repair capacity and contribute to increased PC risk [25]. We could explain the absence of the association between XPC polymorphisms and Gleason score of PC in Tunisian population in comparison to the Indian population by the fact that these two populations were not exposed to the same environmental risk factors. The correlation between XPC polymorphisms, lifestyle factors (tobacco status, alcohol consumption, exposition to the professional risk factor) and XPC gene polymorphisms does not report any significant difference. These results suggest that the severity and the progression of prostate cancer in our population don't depend on environmental and genetic risk factors. The role of these risk factors was only limited to the tumor initiation, however, tumor progression is directly associated with somatic alteration.

Conclusion

In this study, we find that the XPC-PAT I/I genotype may be involved in the susceptibility to PC in the Tunisian population. However, this genotype was not associated with tumors severity.

Acknowledgements The team work would like to express their thanks and gratitude to the medical team of Urology department, Charles Nicolle Hospital, Tunis—Tunisia.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This project was approved by a Charles Nicolle ethical committee, Tunis; Tunisia.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Bello AP, Masip TC (2014) Prostate cancer epidemiology. *Arch Esp de Urol* 67(5):373–382
- Curado MP, Shin HR, Storm H, Heanue M, Boyle P (2007) Cancer incidence in five continents IARC scientific publications
- Forrest MS, Edwards SM, Houlston R, Kote-Jarai Z, Key T, Allen N, Knowles MA, Turner F, Ardern-Jones A, Murkin A, Williams S, Oram R, collaborators C-UBUpcs, Bishop DT, Eeles RA (2005) Association between hormonal genetic polymorphisms and early-onset prostate cancer. *Prostate Cancer Prostat Dis* 8:95. <https://doi.org/10.1038/sj.pcan.4500785>
- Gong Z, Agalliu I, Lin DW, Stanford JL, Kristal AR (2008) Cigarette smoking and prostate cancer-specific mortality following diagnosis in middle-aged men. *Cancer Causes Control: CCC* 19(1):25–31. <https://doi.org/10.1007/s10552-007-9066-9>
- Gong Z, Kristal AR, Schenk JM, Tangen CM, Goodman PJ, Thompson IM (2009) Alcohol consumption, finasteride, and prostate cancer risk: results from the prostate cancer prevention trial. *Cancer* 115(16):3661–3669. <https://doi.org/10.1002/cncr.24423>
- Rozet F, Hennequin C, Beauval JB, Beuzebec P, Cormier L, Fromont G, Mongiat-Artus P, Ouzzane A, Ploussard G, Azria D, Brenot-Rossi I, Cancel-Tassin G, Cussenot O, Lebre T, Rebillard X, Soulié M, Renard-Penna R, Méjean A (2016) Recommendations on onco-urologie 2016–2018 du CCAFU: cancer de la prostate. *Progrès en Urol* 27:S95–S143. [https://doi.org/10.1016/s1166-7087\(16\)30705-9](https://doi.org/10.1016/s1166-7087(16)30705-9)
- He J, Shi TY, Zhu ML, Wang MY, Li QX, Wei QY (2013) Associations of Lys939Gln and Ala499Val polymorphisms of the XPC gene with cancer susceptibility: a meta-analysis. *Int J Cancer* 133(8):1765–1775. <https://doi.org/10.1002/ijc.28089>
- Liu Y, Wang H, Lin T, Wei Q, Zhi Y, Yuan F, Song B, Yang J, Chen Z (2012) Interactions between cigarette smoking and XPC-PAT genetic polymorphism enhance bladder cancer risk. *Oncol Rep* 28(1):337–345. <https://doi.org/10.3892/or.2012.1759>
- Brown KL, Roginskaya M, Zou Y, Altamirano A, Basu AK, Stone MP (2010) Binding of the human nucleotide excision repair proteins XPA and XPC/HR23B to the 5R-thymine glycol lesion and structure of the cis-(5R,6S) thymine glycol epimer in the 5'-GTgG-3' sequence: destabilization of two base pairs at the lesion site. *Nucleic Acids Res* 38(2):428–440. <https://doi.org/10.1093/nar/gkp844>
- Jiang X, Zhou L-t, Zhang S-c, Chen K (2012) XPC polymorphism increases risk of digestive system cancers: current evidence from A meta-analysis. *Chin J Cancer Res* 24(3):181–189. <https://doi.org/10.1007/s11670-012-0181-0>
- Zhu Y, Yang H, Chen Q, Lin J, Grossman HB, Dinney CP, Wu X, Gu J (2008) Modulation of DNA damage/DNA repair capacity

- by XPC polymorphisms. *DNA Repair* 7(2):141–148. <https://doi.org/10.1016/j.dnarep.2007.08.006>
12. Marin MS, Lopez-Cima MF, Garcia-Castro L, Pascual T, Marron MG, Tardon A (2004) Poly (AT) polymorphism in intron 11 of the XPC DNA repair gene enhances the risk of lung cancer. *Cancer Epidemiol, Biomark Prev* 13 (11 Pt 1):1788–1793
 13. Qiao Y, Spitz MR, Shen H, Guo Z, Shete S, Hedayati M, Grossman L, Mohrenweiser H, Wei Q (2002) Modulation of repair of ultraviolet damage in the host-cell reactivation assay by polymorphic XPC and XPD/ERCC2 genotypes. *Carcinogenesis* 23(2):295–299
 14. Sak SC, Barrett JH, Paul AB, Bishop DT, Kiltie AE (2005) The polyAT, intronic IVS11-6 and Lys939Gln XPC polymorphisms are not associated with transitional cell carcinoma of the bladder. *Br J Cancer* 92(12):2262–2265. <https://doi.org/10.1038/sj.bjc.6602616>
 15. Zhang L, Zhang Z, Yan W (2005) Single nucleotide polymorphisms for DNA repair genes in breast cancer patients. *Clin Chim Acta* 359(1–2):150–155. <https://doi.org/10.1016/j.cccn.2005.03.047>
 16. Hirata H, Hinoda Y, Tanaka Y, Okayama N, Suehiro Y, Kawamoto K, Kikuno N, Majid S, Vejdani K, Dahiya R (2007) Polymorphisms of DNA repair genes are risk factors for prostate cancer. *Eur J Cancer (Oxford, England 1990)* 43(2):231–237. <https://doi.org/10.1016/j.ejca.2006.11.005>
 17. Wu H, Lv Z, Wang X, Zhang L, Mo N (2015) Lack of association between XPC Lys939Gln polymorphism and prostate cancer risk: an updated meta-analysis based on 3039 cases and 3253 controls. *Int J Clin Exp Med* 8(10):17959–17967
 18. Mirecka A, Paszkowska-Szczur K, Scott RJ, Gorski B, van de Wetering T, Wokolorczyk D, Gromowski T, Serrano-Fernandez P, Cybulski C, Kashyap A, Gupta S, Golab A, Slojewski M, Sikorski A, Lubinski J, Debniak T (2014) Common variants of xeroderma pigmentosum genes and prostate cancer risk. *Gene* 546(2):156–161. <https://doi.org/10.1016/j.gene.2014.06.026>
 19. Zou Y-F, Tao J-H, Ye Q-L, Pan H-F, Pan F-M, Su H, Ye D-Q (2013) Association of XPC gene polymorphisms with susceptibility to prostate cancer: evidence from 3936 subjects. *Genet Test Mol Biomark* 17(12):926–931. <https://doi.org/10.1089/gtmb.2013.0267>
 20. Evans GA (1990) *Molecular cloning: a laboratory manual*. 2nd edn. Volumes 1, 2, and 3. *Current protocols in molecular biology*. *Cell* 61 (1):17–18. [https://doi.org/10.1016/0092-8674\(90\)90210-6](https://doi.org/10.1016/0092-8674(90)90210-6)
 21. Excoffier L, Laval G, Schneider S (2005) Arlequin (version 3.0): an integrated software package for population genetics data analysis. *Evol Bioinf Online* 1:47–50
 22. Agalliu I, Kwon EM, Salinas CA, Koopmeiners JS, Ostrander EA, Stanford JL (2010) Genetic variation in DNA repair genes and prostate cancer risk: results from a population-based study. *Cancer Causes Control* 21(2):289–300. <https://doi.org/10.1007/s10552-009-9461-5>
 23. Yoshino Y, Takeuchi S, Katoh T, Kuroda Y (2016) XPC intron11 C/A polymorphism as a risk factor for prostate cancer. *Environ Health Prev Med* 21(2):100–104. <https://doi.org/10.1007/s12199-015-0505-z>
 24. Dai QS, Hua RX, Zhang R, Huang YS, Hua ZM, Yun CT, Zeng RF, Long JT (2013) Poly (AT) deletion/insertion polymorphism of the XPC gene contributes to urinary system cancer susceptibility: a meta-analysis. *Gene* 528(2):335–342. <https://doi.org/10.1016/j.gene.2013.06.092>
 25. Mandal RK, Gangwar R, Kapoor R, Mittal RD (2012) Polymorphisms in base-excision and nucleotide-excision repair genes and prostate cancer risk in north Indian population. *Indian J Med Res* 135:64–71
 26. Mittal RD, Mandal RK (2012) Genetic variation in nucleotide excision repair pathway genes influence prostate and bladder cancer susceptibility in North Indian population. *Indian J Hum Genet* 18(1):47–55. <https://doi.org/10.4103/0971-6866.96648>
 27. Wu X, Gu J, Grossman HB, Amos CI, Etzel C, Huang M, Zhang Q, Millikan RE, Lerner S, Dinney CP et al (2006) Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. *Am J Hum Genet* 78(3):464–479
 28. Zhu Y, Lai M, Yang H, Lin J, Huang M, Grossman HB, Dinney CP, Wu X (2007) Genotypes, haplotypes and diplotypes of XPC and risk of bladder cancer. *Carcinogenesis* 28(3):698–703
 29. Kahnemouei SA, Narouie B, Sotoudeh M, Mollakouchehian MJ, Simforoosh N, Ziaee SA, Samzadeh M, Afshari M, Jamaldini SH, Imeni M, Hasanzad M (2016) Association of XPC Gene Polymorphisms with Prostate Cancer Risk. *Clin Lab* 62(6):1009–1015

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.