Association of polymorphisms in nucleotide excision repair pathway genes with susceptibility to cutaneous melanoma

Vztah mezi polymorfizmy genů nukleotidové exciní reparace a náchylností ke kožnímu melanomu

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Summary

Background: The effects of single nucleotide polymorphisms (SNPs) at nucleotide excision repair (NER) pathway on susceptibility to cutaneous melanoma (CM) are of great interest. To date, several epidemiological studies have evaluated whether the *XPC, XPD, XPG* and *XPF* polymorphisms are associated with CM. However, those studies results are controversial or inconclusive. Therefore, we conducted a study to evaluate the association of seven frequently investigated NER pathway polymorphisms with CM risk. ***Methods:*** A total of 150 patients diagnosed with CM and 150 healthy controls were enrolled in the study. Seven SNPs in the NER pathway including *XPC* (Lys939Gln and Ala499Val), *XPD* (Lys157Gln, Asp272Asn, and Arg751Arg), *XPG* (Asp1104His) and *XPF* (Arg415Gln) were analyzed by polymerase chain reaction restriction fragment length polymorphism assay. ***Results:*** There was no a significant association between *XPC* Lys939Gln, Ala499Val; *XPD* Asp272Asn, Arg751Arg, Arg751Arg; *XPF* Arg415Gln; and *XPG* Asp1104His polymorphisms and an increased risk of CM. ***Conclusions:*** This study results revealed that the *XPC, XPD, XPG* and *XPF* polymorphisms were not risk factor for susceptibility to CM. However, more well-designed with larger sample size studies in different populations are necessary to further evaluate and validate our results. Future studies which take into account gene-gene and gene-environment interactions are warranted for more precise evidence and further elucidation of the underlying mechanism of CM.

Key words

cutaneous melanoma – nucleotide excision repair – single nucleotide polymorphism – association

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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Souhrn

Východiska: Účinky jednonukleotidových polymorfizmů (single nucleotide polymorphisms – SNPs) genů nukleotidové excizní reparace (nucleotide excision repair – NER) na náchylnost ke kožnímu melanomu (cutaneous melanoma – CM) jsou předmětem velkého zájmu. V současné době je v několika epidemiologických studiích hodnoceno, zda polymorfizmy *XPC, XPD, XPG* a *XPF* souvisí s CM. Výsledky těchto studií jsou ale kontroverzní nebo nevedou k jednoznačnému závěru. Proto jsme provedli studii s cílem zhodnotit vztah mezi sedmi často zkoumanými polymorfizmy dráhy NER a rizikem CM. ***Metody:*** Do studie bylo zařazeno celkem 150 patients s diagnózou CM a 150 zdravých kontrol. Sedm SNPs dráhy NER vč. *XPC* (Lys939Gln a Ala499Val), *XPD* (Lys157Gln, Asp272Asn a Arg751Arg), *XPG* (Asp1104His) a *XPF* (Arg415Gln) bylo analyzováno stanovením polymorfizmu délky štěpných fragmentů pomocí polymerázové řetězové reakce. ***Výsledky:*** Mezi polymorfizmy *XPC* Lys939Gln, Ala499Val, *XPD* Asp272Asn, Arg751Arg, Arg751Arg, *XPF* Arg415Gln a *XPG* Asp1104His a zvýšeným rizikem CM nebyl zjištěn významný vztah. ***Závěry:*** Tato studie odhalila, že polymorfizmy *XPC, XPD, XPG* a *XPF* nebyly pro náchylnost k CM rizikovým faktorem. Pro další hodnocení a validaci našich výsledků je třeba více studií s dobrým designem a vyšším počtem subjektů v různých populacích. Přesnější důkazy a další objasnění vlastního mechanizmu CM přinesou v budoucnosti studie, které budou brát v úvahu interakce mezi geny jako takovými a mezi geny a prostředím.

Klíčová slova

kožní melanom – nukleotidová excizní reparace – jednonukleotidový polymorfizmus – vztah

Introduction

Each year, tens of millions of cases are diagnosed with a malignancy worldwide, and more than half of them eventually die from it [1–5]. Cutaneous melanoma (CM) is an aggressive tumor of melanocytes in the skin [6]. CM causes more deaths than any other skin tumor, and the annual incidence of this disease has increased dramatically, which makes it one of the fastest growing cancers worldwide [7]. Estimates of the worldwide incidence revealed 232,000 new cases and 55,000 deaths for CM in 2012, with a 15th place among most common cancers worldwide [8]. The incidence and mortality rates of cutaneous melanoma differ widely by ethnic background [9]. In the United States, CM is among the top ten of leading cancer sites with a 5th place for men and a 6th place for women [10]. In less than 10 years, melanoma treatment has been revolutionized. However, the outcome for melanoma is highly dependent on the stage of the disease [6,11]. The etiology of melanoma is multifactorial and includes both environmental and genetic factors [6]. The most important risk factor for developing melanoma is exposure to skin color and ultraviolet radiation intensity [12]. Approximately 10% of CM cases have affected relatives, thus positive family history of CM may be associated with an increased risk of CM [13]. Recent advances in molecular genetic technology, notably next-generation sequencing (NGS), have led to the identification of multiple loci involved in the development and progression of CM such as genetic variations at nucleotide excision repair (NER) pathway [14,15].

The human genome is frequently subjected to damage from several deleterious environmental agents, e. g. ultraviolet (UV) light, chemotherapeutic agents or radiation, and endogenous weak mutagens, e. g. reactive oxygen species and metabolites like alkylating agents [16,17]. NER is the major mechanism in the process of DNA repair, which is mainly implicated in the replacement of bulky and helix distorting adducts with newly synthesized DNA segments. The major proteins involved in NER include XPA, XPC, XPD, XPE, XPF, XPG and ERCC [18]. Previously published epidemiological studies have indicated the association between single nucleotide polymorphisms (SNPs) in NER pathway genes and development of different cancers [19,20]. Hence, genetic alteration of NER-related genes may be closely related to the occurrence and development of CM [21–23]. In this study, we have evaluated association of seven potential functional polymorphisms including *XPC* (Lys939Gln and Ala499Val), *XPD* (Lys157Gln, Asp272Asn, and Arg751Arg), *XPG* (Asp1104His) and *XPF* (Arg415Gln) with a risk of CM.

Materials and methods

Subjects

A total of 150 patients diagnosed with CM were enrolled between February 2015 and September 2018. The cases were eligible if they had newly diagnosed and histologically confirmed CM without undergoing radiotherapy and chemotherapy treatment. During the same period, 150 age- and gender-matched healthy subjects were randomly selected as controls from the same centers. All the research subjects were unrelated ethnic Iranian population from six different cities. The study was reviewed and approved by the ethical review boards and a written informed consent was received from the guardian of each participant.

SNPs selection and genotyping

Seven potentially functional polymorphisms widely evaluated in various types of cancer including *XPC* (Lys939Gln and *XPC* Ala499Val), *XPD* (Asp272Asn, Arg751Arg and Arg751Arg), *XPF* (Arg415Gln) and *XPG* (Asp1104His) genes were selected. The selected SNPs had a high mutation frequency and were located in the noncoding or coding regions of the NER pathway. Genomic DNA was extracted from 2 mL of peripheral blood of cases and controls using the YTA Blood DNA Kit (Yekta-Tajhiz Azma, Tehran, Iran) according to the manufacturer's instructions and the samples were frozen at –80 °C. Then, the selected SNPs were genotyped using polymerase chain reaction-restriction fragment length polymorphism assay as described previously [24–29]. The volume of PCR reaction was performed 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 $MgCl_2$, 0.20 mM of dNTP, and 1U of Taq DNA polymerase (Promega, USA). The PCR fragments of the selected SNPs were subsequently digested with their specific restriction enzyme. Then, the digested products were separated by electrophoresis on EtBr stained agarose gel and visualized under UV light.

Statistical analysis

We used the χ^2 test to evaluate the differences in the frequency distributions of the genotypes between CM cases and healthy subjects. The genotype distributions in the study population were tested to ensure conformity with Hardy-Weinberg equilibrium by means of Pearson's χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the correlations between the three polymorphisms and neuroblastoma susceptibility with the unconditional multivariate logistic regression analysis. All statistical analyses were performed with SPSS 21.0 package (SPSS Inc., Chicago, IL, USA). The P-value was considered statistically significant at < 0.05.

Results

The clinical and epidemiological parameters of CM cases and controls were presented in Tab. 1. The mean ages of patients with CM and healthy subjects were 52.11±16.4 and 51.18±17.0 years, respectively. No significant differences were observed in terms of age (P = 0.684) and gender (P = 0.816) between the case and the control groups. The genotype frequencies of the three polymorphisms are shown in Tab. 2. Genotype frequency distributions of the two SNPs in controls were in agreement with the Hardy-Weinberg equilibrium (HWE) (P = 0.492 for *XPC* Lys939Gln; P = 0.698 for *XPC* Ala499Val; P = 0.351 for *XPD* Asp272Asn; P = 0.371 for *XPD* Arg751Arg; P = 0.763 for *XPD* Arg751Arg; P = 0.889 for *XPF* Arg415Gln; and P = 0.111 for *XPG* Asp1104His). Our results showed that none of the *XPC* (Lys939Gln and Ala499Val), *XPD* (Lys157Gln, Asp272Asn, and Arg751Arg), *XPG* Asp1104His, and *XPF* Arg415Gln polymorphisms was significantly associated with an increased risk of CM.

Tab. 1. Clinical and demographic characteristics of cases with cutaneous melanoma and healthy subjects.

Variables	Cases (N = 150)	Controls (N = 150)	P-value
age (years, mean ± SD)	52.11 ± 16.4	51.18±17.0	0.684
gender			
female	83 (55.3)	85(56.7)	0.816
male	67 (44.7)	65(43.3)	
histological subtypes			
superficial spreading melanoma	96 (64.0)		
nodular melanoma	22 (14.7)		
lentigo maligna melanoma	16 (10.7)		
acral lentiginous melanoma	12 (8.0)		
other	4 (2.6)		
tumor thickness			
≤ 1 mm	94 (62.7)		
> 1 mm	56 (37.3)		
ulceration at primary lesion			
yes	43 (28.7)		
no	107 (71.3)		
sentinel lymph node metastasis			
yes	29 (19.3)		
no	121 (80.7)		

Discussion

To the best knowledge, this is the first study to evaluate the association of *XPC* (Lys939Gln and Ala499Val), *XPD* (Lys157Gln, Asp272Asn, and Arg751Arg), *XPG* Asp1104His and *XPF* Arg415Gln polymorphisms with susceptibility to CM in Iranian population. The current case-control study results revealed that none of the *XPC* Lys939Gln, *XPC* Ala499Val; *XPD* Asp272Asn, Arg751Arg and Arg751Arg; *XPF* Arg415Gln and *XPG* Asp1104His polymorphisms were associated with an increased risk of CM. Povey et al evaluated the association of DNA repair gene polymorphisms and genetic predisposition to CM in a Scottish population. Their results showed that polymorphisms at *ERCC1* and *XPF* genes that act together in a complex to make an incision to the 5′ side of a DNA lesion were associated with CM risk [30].

The *XPC* gene plays an important role in the early step of Global Genome Repair pathway (GGR), especially in damage recognition, open complex formation, and reparation via a complex composed by HR23B-XPC-CEN during GGR pathway [31,32]. *XPC* gene is localized on chromosome 3p25 and consists of 16 exons and 15 introns. To date, more than 2,582 polymorphic variants in the *XPC* gene have been identified [33]. Two common polymorphic loci of the *XPC* gene, rs2228000 (G>A, Ala499Val) and rs2228001 (G>T, Lys939Gln) have been investigated in association with the risk of CM. Our results showed that *XPC* Ala499Val and Lys939Gln polymorphisms were not associated with CM risk in our population, confirming the results reported for the same polymorphism by Povey et al in the Scottish population. Previous meta-analyses also reported inconsistent results about the association between these polymorphisms and risk of CM [30]. In a meta-analysis of eight studies with 4,631 CM cases

Tab. 2. Genotype and allele frequencies of the polymorphisms at nucleotide excision repair pathway and cutaneous melanoma risk.

SNPs	Genotypes/ Alleles	Frequency		Odds ratio		
		Cases (N = 150)	Controls (N = 150)	OR	95% CI	P-value
XPC Lys939Gln (A>C)	AA	55 (28.7)	49 (28.0)	Ref.		
	AC	69 (50.0)	77 (53.3)	0.808	0.513–1.271	0.356
	CC	26 (21.3)	24 (18.7)	1.101	0.600–2.021	0.757
	A	179 (53.7)	175 (54.7)	Ref.		
	C	121 (46.3)	125 (45.3)	0.946	0.683–1.310	0.740
XPC Ala499Val (G>A)	GG	80 (27.3)	79 (31.3)	Ref.		
	GA	57 (48.0)	61 (46.0)	0.894	0.563–1.422	0.636
	AA	13 (24.7)	10 (22.7)	1.328	0.564–3.131	0.516
	G	217 (51.3)	219 (54.3)	Ref.		
	A	83 (48.7)	81 (46.7)	1.034	0.722–1.481	0.855
XPD Lys157Gln (A>C)	AA	43 (28.7)	42 (28.0)	Ref.		
	AC	75 (50.0)	80 (53.3)	0.875	9.556–1.377	0.564
	CC	32 (21.3)	28 (18.7)	1.182	0.670–2.083	0.577
	A	161 (53.7)	164 (54.7)	Ref.		
	C	139 (46.3)	136 (45.3)	1.041	0.755–1.435	0.806
XPD Asp272Asn (G>A)	GG	41 (27.3)	47 (31.3)	Ref.		
	GA	72 (48.0)	69 (46.0)	1.084	0.688–1.705	0.729
	AA	37 (24.7)	34 (22.7)	1.117	0.656–1.903	0.407
	G	161 (53.7)	157 (52.3)	Ref.		
	A	139 (43.3)	143 (47.6)	1.128	0.818–1.554	0.736
XPD Arg751Arg (C>A)	CC	48 (32.0)	42 (28.0)	Ref.		
	CA	65 (43.3)	73 (48.7)	0.807	0.512–1.271	0.354
	AA	37 (24.7)	35 (23.3)	1.076	0.633–1.828	0.787
	C	161 (53.7)	157 (52.3)	Ref.		
	A	139 (43.3)	143 (47.6)	0.948	0.688–1.306	0.744
XPG Asp1104His (A>C)	AA	79 (52.7)	81 (54.0)	Ref.		
	AC	53 (35.3)	58 (38.7)	0.867	0.542–1.385	0.550
	CC	18 (12.0)	11 (7.3)	1.723	0.784–3.785	0.175
	A	211 (70.3)	220 (73.3)	Ref.		
	C	89 (29.7)	80 (26.7)	1.160	0.812–1.666	0.414
XPF Arg415Gln (G>A)	GG	69 (46.0)	81 (54.0)	Ref.		
	GA	61 (40.7)	53 (35.3)	1.254	0.786–2.001	0.342
	AA	20 (13.3)	16 (10.7)	1.288	0.640–2.595	0.478
	G	199 (66.3)	215 (71.7)	Ref.		
	A	101 (33.7)	85 (28.3)	1.284	0.907–1.816	0.158

CI – confidence interval, OR – odds ratio, SNPs – single nucleotide polymorphisms

and 5,111 controls, Jiang et al evaluated the association of *XPC* Lys939Gln polymorphism with CM risk. Their pooled data suggested that *XPC* Lys939Gln polymorphism was not significantly associated with CM risk [32]. In a meta-analysis, Zhou et al found an association between *XPC* Lys939Gln polymorphism and CM risk [34].

The human *XPD* gene is located at chromosome 19q13.3, possesses both single strand DNA-dependent ATPase and 5′-3′ DNA helicase activities and participates in DNA unwinding during NER. It is reported that genetic variants at *XPD* gene reduced the helicase activity, causing repair activity of NER pathway in a lower DNA and increasing cancer susceptibility [35]. Our study results failed to show an association between three Asp272Asn, Arg751Arg, Asp272Asn polymorphisms at *XPD* gene and susceptibility to CM. The Scottish study involving 596 CM patients and 441 population-based controls also reported no association between the *XPD* Lys751Gln polymorphism and CM risk [30]. Other two studies in Poland and UK did not report an association between single *XPD* polymorphisms and CM [36,37]. However, Debniak et al found that *XPD* haplotypes were associated with susceptibility to CM in a Polish population [37]. In a meta-analysis of eleven studies with 5,961 cases and 8,669 controls, Sun et al evaluated an association between *XPD* Lys751Gln polymorphism and CM among Caucasians. Their pooled data suggest that there was no evidence for a major role of *XPD/ERCC2* Lys751Gln polymorphism in the pathogenesis of CM among Caucasians [38]. However, in other meta-analysis including 3,492 cases and 5,381 controls, Liu et al revealed that the *XPD* Lys751Gln polymorphism has contributed to CM susceptibility, and *XPD* is a possible drug target [39]. Zhu et al assessed an association of *XPD* Lys751Gln and Asp312Asn polymorphisms with skin cancer risk in a meta-analysis. They have reported that *XPD* Lys751Gln polymorphism was not associated with a risk of skin cancer under all genetic models. Their stratified analysis by tumor type revealed that *XPD* Lys751Gln polymorphism was not associated with an increased risk of non-melanoma skin cancer, but was significantly associated with an increased risk of CM. However, they have showed that *XPD* Asp312Asn polymorphism is not significantly associated with a risk of non-melanoma and melanoma skin cancers [40].

The human *XPG* gene encodes a structure-specific endonuclease that cuts the damaged DNA strand 3′ to the lesion near the junction between the unpaired damaged strand and downstream undamaged duplex DNA [24,41] and *XPG* has a noncatalytic role in NER which is necessary in the incision complex to permit the *XPF/ERCC1* heterodimer to make the 5′-cut [42]. The human *XPG* gene is located on chromosome 13q32-33, encodes a protein with a predicted molecular mass of 133 kDa [43]. Previous studies indicated that *XPG* Asp1104His polymorphism can influence the DNA repair ability for tobacco and alcohol-induced DNA damage, thereby increasing the susceptibility to cancer. In this study, we have not found a significant association between *XPG* rs17655 polymorphism and development of CM. In a meta-analysis of eight published case-control studies with 5,212 cases and 7,045 controls, Xu et al evaluated the association of *XPG* Asp1104His polymorphism with CM susceptibility. Their results revealed that the *XPG* Asp1104His polymorphism was a risk factor for CM susceptibility [41]. However, Li et al did not found evidence of an association between *XPD* genotypes and development of CM [44].

The human *XPF* gene is involved in the 5′ incision made during nucleotide excision repair and maintaining chromosome stability [45,46]. It is located at chromosome 16p13.12, consists of 11 exons and spanning about 28.2 kb [42]. Further, *XPF/ERCC1* heterodimer participates in the repair of „crosslink" damage that harmfully links the two DNA strands [47]. Our results failed to show a significant association between *XPF* Arg415Gln polymorphism and CM risk. However, Oliveira et al revealed in a case-control study that polymorphisms at XPC, XPF, TP53 and GSTP1 pathways of the DNA repair genes are important determinants of CM in individuals from south-eastern Brazil [48]. Moreover, Gomez et al found that inherited abnormalities in DNA repair pathway related to *XPF* Arg415Gln polymorphism might be a prognostic factor for overall survival of Brazilian CM patients [49]. Povey et al also supported that *XPF* Arg415Gln polymorphism is associated with a risk of CM Scottish patients [30].

Conclusions

This study results showed that all the seven polymorphisms at *XPC* (Lys939Gln and Ala499Val), *XPD* (Lys157Gln, Asp272Asn, and Arg751Arg), *XPG* (Asp1104His) and *XPF* (Arg415Gln) genes may not associate with an increased risk of CM. However, more well-designed studies with larger sample size in different ethnicities are necessary to further evaluate and verify our results. Future studies which take into account gene-gene and gene-environment interactions are warranted for more precise evidence and further elucidation of the underlying mechanism of CM.

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Authors' contributions: FA and MAG conceptualized the study. SK and HN designed the study and the interview guide. Data analysis was done by SAD and HN. Manuscript was written and critically reviewed by GRD, HN, EA and AE. All authors read and approved the final manuscript.

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