The role of *CCNH* Val270Ala (rs2230641) and other nucleotide excision repair polymorphisms in individual susceptibility to well-differentiated thyroid cancer

LUÍS S. SANTOS[1,2*], BRUNO C. GOMES[1*], RITA GOUVEIA[1], SUSANA N. SILVA[1], ANA P. AZEVEDO[1,3], VANESSA CAMACHO[1], ISABEL MANITA[4], OCTÁVIA M. GIL[1,5], TERESA C. FERREIRA[6], EDWARD LIMBERT[6], JOSÉ RUEFF[1] and JORGE F. GASPAR[1]

[1]Department of Genetics, Faculty of Medical Sciences, Universidade Nova de Lisboa (UNL), Lisbon; [2]Health Sciences Institute, Universidade Católica Portuguesa (UCP), Viseu; [3]Department of Clinical Pathology, Hospital de S. Francisco Xavier, Lisbon; [4]Unit of Endocrinology, Hospital Garcia de Orta, Almada; [5]Unit of Radiological Protection and Safety-Technological and Nuclear Campus, Instituto Superior Técnico, Universidade Técnica de Lisboa (UTL), Loures; [6]Department of Nuclear Medicine, Instituto Português de Oncologia de Lisboa, Lisbon, Portugal

Received May 3, 2013; Accepted July 5, 2013

DOI: 10.3892/or.2013.2702

Abstract. Well-differentiated thyroid cancer (DTC) is the most common form of thyroid cancer (TC); however, with the exception of radiation exposure, its etiology remains largely unknown. Several single nucleotide polymorphisms (SNPs) have previously been implicated in DTC risk. Nucleotide excision repair (NER) polymorphisms, despite having been associated with cancer risk at other locations, have received little attention in the context of thyroid carcinogenesis. In order to evaluate the role of NER pathway SNPs in DTC susceptibility, we performed a case-control study in 106 Caucasian Portuguese DTC patients and 212 matched controls. rs2230641 (*CCNH*), rs2972388 (*CDK7*), rs1805329 (*RAD23B*), rs3212986 (*ERCC1*), rs1800067 (*ERCC4*), rs17655, rs2227869 (*ERCC5*), rs4253211 and rs2228529 (*ERCC6*) were genotyped using TaqMan® methodology, while conventional PCR-RFLP was employed for rs2228000 and rs2228001 (*XPC*). When considering all DTC cases, only rs2230641 (*CCNH*) was associated with DTC risk; a consistent increase in overall DTC risk was observed for both the heterozygous genotype (OR=1.89, 95% CI=1.14-3.14) and the variant allele carriers (OR=1.79, 95% CI=1.09-2.93). Histological stratification analysis confirmed an identical effect on follicular TC (OR=2.72, 95% CI=1.19-6.22, for heterozygous; OR=2.44, 95% CI=1.07-5.55, for variant allele carriers). Considering papillary TC, the rs2228001 (*XPC*) variant genotype was associated with increased risk (OR=2.33, 95% CI=1.05-5.16), while a protective effect was observed for rs2227869 (*ERCC5*) (OR=0.26, 95% CI=0.08-0.90, for heterozygous; OR=0.25, 95% CI=0.07-0.86, for variant allele carriers). No further significant results were observed. Our results suggest that NER polymorphisms such as rs2230641 (*CCNH*) and, possibly, rs2227869 (*ERCC5*) and rs2228001 (*XPC*), may influence DTC susceptibility. However, larger studies are required to confirm these results.

Correspondence to: Professor Jorge Francisco Gaspar, Department of Genetics, Faculty of Medical Sciences, Universidade Nova de Lisboa (UNL), Rua da Junqueira 100, P-1349-008 Lisbon, Portugal
E-mail: jorge.gaspar@fcm.unl.pt

*Contributed equally

Key words: CCNH, DNA repair, genetic susceptibility, nucleotide excision repair, single nucleotide polymorphisms, well-differentiated thyroid cancer

Introduction

Thyroid cancer (TC) is a rare neoplasia, but is the most frequent endocrine malignancy (1). In general, it originates from thyroid follicular cells and its most common histological types are papillary carcinoma (≈70-80%) and follicular carcinoma (≈10-20%) (2). Papillary and follicular TC are often categorized together as non-medullary well-differentiated thyroid cancer (DTC), and, in contrast to undifferentiated (anaplastic) TC, have indolent behaviour and can be treated with high survival rates, particularly if they are localized and small-sized (1). TC can occur in any age group but its incidence increases with age (1). This type of cancer (particularly DTC) is 3 times more likely to occur in women than in men and, in the past 2 decades, its incidence has increased (1). The best-established cause of thyroid carcinogenesis is exposure to ionizing radiation, although other candidate risk factors such as dietary iodine deficiency, hormonal factors, benign thyroid conditions and familial history have also been noted (2).

DTC frequency is significantly higher in relatives (particularly first-degree) of DTC patients compared to the general population (2,3). However, familial DTC accounts for only a minor percentage of cases (2), suggesting that other genetic risk factors could be involved. Identifying such individual genetic differences so that these may be used as genetic

susceptibility markers for DTC in the remaining sporadic cases is therefore an important challenge. In line with this, several DNA polymorphisms in genes involved in endobiotic or xenobiotic metabolism (including GST and CYP superfamilies), in hormonal and iodine metabolism (such as *TG*), in cell-cycle control and regulation of apoptosis (such as *TP53*), in kinase-dependent signaling pathways (such as *RET*) and in DNA repair (among others) have been associated with differential susceptibility to DTC [reviewed in reference (3)]. The first genome-wide association study (GWAS) performed on TC identified 2 other polymorphisms located near the *FOXE1* (*TTF-2*) and *NKX2-1* (*TTF-1*) genes (which encode for thyroid-specific transcription factors) as strong genetic risk markers of sporadic DTC in European populations (4).

Since patients with papillary TC present a significant increase in DNA damage (5) and DNA repair mechanisms are important in correcting such damage, it is reasonable to assume that defective DNA repair capacity may contribute to DTC risk. Variants in DNA repair genes may affect the DNA repair capacity and, in fact, several single nucleotide polymorphisms (SNPs) in almost all DNA repair pathways have been shown to incrementally contribute to cancer risk (6). Regarding TC, polymorphisms in DNA repair genes such as *XRCC1* (7-9) and possibly *MUTYH* (10) (BER pathway), *Ku80* (11) (NHEJ pathway), *BRCA1* (12), *XRCC3* and possibly *RAD51* (13) (HR pathway) have been associated with either TC or, more specifically, DTC risk [reviewed in references (3,14,15)].

Nucleotide excision repair (NER) is a versatile DNA repair mechanism capable of repairing UV light-induced lesions, bulky DNA adducts, distorting interstrand crosslinks and even certain oxidative lesions (16). A significant association between an *ERCC2* haplotype (rs13181/rs1799793) and TC risk (mainly papillary) was previously reported by our team (17), suggesting that NER polymorphisms may also be relevant for thyroid carcinogenesis. However, to our knowledge, no other published study has thus far focused on a possible role of NER pathway SNPs in DTC susceptibility.

Therefore, we carried out an exploratory hospital-based case-control study in a Caucasian Portuguese population to evaluate the potential modifying role of a panel of 11 NER pathway SNPs (*CCNH* rs2230641, *CDK7* rs2972388, *RAD23B* rs1805329, *ERCC1* rs3212986, *ERCC4* rs1800067, *ERCC5* rs17655 and rs2227869, *ERCC6* rs4253211 and rs2228529 and *XPC* rs2228000 and rs2228001) on the individual susceptibility to non-familial DTC.

Materials and methods

Study subjects. This study included 106 Caucasian Portuguese DTC patients without familial history of TC, previous neoplastic pathology and recent blood transfusion. Patients were recruited in the Department of Nuclear Medicine of the Portuguese Oncology Institute of Lisbon, where they received Iodine-131 treatment. Histological diagnosis was confirmed for all cases. For each case, 2 age- (±2 years) and gender-matched controls were recruited. Controls (n=212), with no previous or current malignant disease and no personal or familiar history of thyroid pathology, were recruited at São Francisco Xavier Hospital, where they were observed for non-neoplastic pathology. Information on demographic characteristics, family history of cancer, lifestyle habits (such as smoking, alcohol drinking) and exposure to ionizing radiation was collected using a questionnaire administered by trained interviewers. Former smokers were considered as non-smokers if they had given up smoking either 2 years before DTC diagnosis or 2 years before their inclusion as controls. The response rate was >95% for cases and controls. The anonymity of patients and controls was guaranteed and written informed consent was obtained from all those involved, prior to blood withdrawal, in agreement with the Declaration of Helsinki. Approval by the institutional ethics boards of the involved institutions was mandatory.

DNA extraction. Peripheral blood samples of all patients and controls were collected into 10 ml heparinized tubes and kept at -80˚C. Genomic DNA was obtained from each sample using a commercially available kit (QIAamp® DNA mini kit; Qiagen) according to the manufacturer's instructions. All DNA samples were stored at -20˚C until analysis.

SNP selection. Publicly available databases such as NCBI (http://www.ncbi.nlm.nih.gov/snp/), Genecards (http://www.genecards.org) and SNP500Cancer (http://variantgps.nci.nih.gov/cgfseq/pages/snp500.do) were used to search for NER polymorphisms. Eligible SNP's had to be located either in a coding or splice region and had to exhibit minor allele frequency (MAF) >0.05 in Caucasian populations. Despite being located on the 3'UTR region, rs3212986 (*ERCC1*) was also selected since it is one of the most extensively studied *ERCC1* SNPs and evidence exists for functional significance (18,19). In total, 9 common nsSNP's, 1 synonymous SNP and 1 SNP located on 3'UTR were selected (Table I).

Genotyping. rs2230641 (*CCNH*), rs2972388 (*CDK7*), rs1805329 (*RAD23B*), rs3212986 (*ERCC1*), rs1800067 (*ERCC4*), rs17655 and rs2227869 (*ERCC5*), rs4253211 and rs2228529 (*ERCC6*) were genotyped by real-time PCR, using TaqMan SNP Genotyping Assays (Applied Biosystems). To assure uniformity in genomic DNA content (2.5 ng/μl) in all samples, DNA was quantified using the fluorimetric Quant-iT™ Picogreen® dsDNA Assay kit (Invitrogen Life Technologies) and a Zenyth 3100 plate reader (Anthos Labtec Instruments), according to the manufacturer's recommendations. PCR was performed in a 7300 Real-Time PCR system thermal cycler (Applied Biosystems). Genotyping assays used are identified in Table I. The amplification conditions consisted of an initial activation step (10 min, 95˚C), followed by ≥40 amplification cycles of denaturation (15 sec, 92˚C) and annealing/extension (60 sec, 60˚C). Allelic discrimination was performed by measuring fluorescence emitted by VIC and FAM dyes in each well (60 sec) and computing the results into the System SDS software version 1.3.1.

rs2228000 and rs2228001 (*XPC*) genotyping was performed by PCR-RFLP. Primer sequences, PCR conditions, PCR product sizes, restriction analysis conditions and expected digestion pattern for each *XPC* genotype have been described elsewhere (20).

Genotyping was repeated for all inconclusive samples. Also, genotype determinations were carried out twice in independent experiments (100% of concordance between

Table I. Selected SNP's and detailed information on the corresponding base and aminoacid exchanges, minor allele frequency and AB assay used for genotyping.

Gene	Location	dbSNP cluster ID (rs no.)	Base change	Aminoacid change	MAF (%)[a]	AB assay ID
CCNH	5q13.3-q14	rs2230641	T→C	Val270Ala	13.8	C_11685807_10
CDK7	5q12.1	rs2972388	T→C	Asn33Asn	40.5	C_1191757_10
RAD23B	9q31.2	rs1805329	C→T	Ala249Val	16.7	C_11493966_10
ERCC1	19q13.32	rs3212986	C→A	-[b]	29.4	C_2532948_10
ERCC4	16p13.3	rs1800067	G→A	Arg415Gln	3.1	C_3285104_10
ERCC5	13q22-q34	rs17655	G→C	Asp1104His	37.7	C_1891743_10
ERCC5	13q22-q34	rs2227869	G→C	Cys529Ser	4.9	C_15956775_10
ERCC6	10q11	rs4253211	G→C	Arg1230Pro	6.4	C_25762749_10
ERCC6	10q11	rs2228529	A→G	Gln1413Arg	15.6	C_16171343_10
XPC	3p25	rs2228000	C→T	Ala499Val	24.8	-[c]
XPC	3p25	rs2228001	A→C	Lys939Gln	34.4	-[c]

[a]Minor allele frequency, according to http://www.ncbi.nlm.nih.gov/projects/SNP/; [b]SNP located on 3'UTR; [c]not applicable (genotyping performed by PCR-RFLP). SNPs, single nucleotide polymorphisms.

experiments) for all samples when SNPs were genotyped by PCR-RFLP and for 10-15% of samples when SNPs were genotyped by real-time PCR.

Statistical analysis. Hardy-Weinberg frequencies for all alleles in patients and controls were analysed using exact probability tests available in Mendel software (V5.7.2) (21). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify the normality of continuous variables and the Levene's test was used to analyze the homogeneity of variances. Differences in genotype frequency, smoking status, age class and gender distributions between patients and controls were evaluated by the χ^2 test. Adjusted odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated using unconditional multiple logistic regression. The model for adjusted OR included terms for gender, age at diagnosis (≤30, 31-49, 50-69 and ≥70 years) and smoking habits (smokers/non-smokers). Male gender, lower age group and non-smokers were considered the reference groups for these variables. For controls, age at diagnosis was defined as the matched case age of diagnosis. All analyses were performed using SPSS 15.0 (SPSS, Inc.).

Table II. General characteristics for the DTC cases (n=106) and control population (n=212).

Characteristics	Controls, n (%)	Cases, n (%)	P-value[c]
Gender			
Male	31 (14.6)	16 (15.1)	0.91
Female	181 (85.4)	90 (84.9)	
Age[a,b]			
≤30	9 (4.2)	4 (3.8)	0.99
31-49	77 (36.3)	39 (36.8)	
50-69	100 (47.2)	49 (46.2)	
≥70	26 (12.3)	14 (13.2)	
Smoking habits			
Non-smokers	172 (81.1)	94 (88.7)	0.12
Smokers	38 (17.9)	12 (11.3)	
Missing	2 (0.9)	0 (0.0)	

[a]Age of diagnosis, for cases; [b]age at the time of diagnosis of the matched case, for controls; [c]P-value determined by χ^2 test (cases vs. control group). DTC, well-differentiated thyroid cancer.

Results

This study comprised 106 DTC patients and 212 age- and gender-matched controls. The histological classification of DTC cases was 73.6% papillary tumours (78 patients) and 26.4% follicular tumours (28 patients). Table II lists the general characteristics of both case and control populations. In the case group, the frequency of females (90 patients) was significantly higher than the frequency of males (16 patients), in accordance with the worldwide estimation for gender distribution in DTC (1). Case and control populations are not statistically different in respect to age distribution, gender and smoking habits.

This report includes a set of 11 SNPs in 8 NER pathway genes (Table I). The MAF and genotypic frequencies of these SNPs, in both DTC cases and controls, are depicted in Table III. All SNPs considered are in Hardy-Weinberg equilibrium (P≥0.05), both in case and control populations, except for rs2972388 (*CDK7*) and rs2228000 (*XPC*) that show a significant deviation in the control (rs2972388) or case population (rs2228000).

Genotypic distributions were compared among cases and controls (Table III). A significant difference was observed only for rs2230641 (*CCNH*) (P=0.04). When considering a dominant model of inheritance, the difference in rs2230641 (*CCNH*) genotypic frequency between cases and controls was even more significant (P=0.02).

Table III. Genotype distribution in case (n=106) and control (n=212) populations and associated DTC risk (adjusted ORs).

	MAF		Genotype frequency			
Genotype	Controls	Cases	Controls, n (%)	Cases, n (%)	P-value[a]	Adjusted OR (95% CI)[b]
CCNH rs2230641			212 (100)	106 (100)		
Val/Val	C: 0.17	C: 0.23	148 (69.8)	60 (56.6)		1 (Reference)
Val/Ala			56 (26.4)	43 (40.6)	**0.04**[c]	**1.89 (1.14-3.14)**[c]
Ala/Ala			8 (3.8)	3 (2.8)		1.01 (0.25-4.03)
Val/Ala + Ala/Ala			64 (30.2)	46 (43.4)	**0.02**[c]	**1.79 (1.09-2.93)**[c]
CDK7 rs2972388			206 (100)	101 (100)		
T/T	C: 0.48	C: 0.42	63 (30.6)	37 (36.6)		1 (Reference)
T/C			88 (42.7)	43 (42.6)	0.42	0.86 (0.50-1.49)
C/C			55 (26.7)	21 (20.8)		0.62 (0.32-1.19)
T/C + C/C			143 (69.4)	64 (63.4)	0.29	0.77 (0.46-1.27)
RAD23B rs1805329			212 (100)	106 (100)		
Ala/Ala	T: 0.16	T: 0.17	150 (70.8)	75 (70.8)		1 (Reference)
Ala/Val			55 (25.9)	27 (25.5)	0.98	0.94 (0.54-1.62)
Val/Val			7 (3.3)	4 (3.8)		1.19 (0.33-4.30)
Ala/Val + Val/Val			62 (29.2)	31 (29.2)	1.00	0.96 (0.57-1.62)
ERCC1 rs3212986			211 (100)	106 (100)		
C/C	A: 0.24	A: 0.21	118 (55.9)	64 (60.4)		1 (Reference)
C/A			83 (39.3)	39 (36.8)	0.61	0.84 (0.51-1.37)
A/A			10 (4.7)	3 (2.8)		0.52 (0.14-1.99)
C/A + A/A			93 (44.1)	42 (39.6)	0.45	0.80 (0.50-1.30)
ERCC4 rs1800067			210 (100)	102 (100)		
Arg/Arg	A: 0.11	A: 0.13	168 (80.0)	77 (75.5)		1 (Reference)
Arg/Gln			38 (18.1)	23 (22.5)	0.65	1.34 (0.74-2.43)
Gln/Gln			4 (1.9)	2 (2.0)		1.05 (0.19-5.98)
Arg/Gln + Gln/Gln			42 (20.0)	25 (24.5)	0.36	1.31 (0.74-2.33)
ERCC5 rs17655			212 (100)	105 (100)		
Asp/Asp	C: 0.30	C: 0.28	106 (50.0)	51 (48.6)		1 (Reference)
Asp/His			85 (40.1)	50 (47.6)	0.12	1.22 (0.75-1.98)
His/His			21 (9.9)	4 (3.8)		0.42 (0.13-1.29)
Asp/His + His/His			106 (50.0)	54 (51.4)	0.81	1.07 (0.67-1.72)
ERCC5 rs2227869			212 (100)	106 (100)		
Cys/Cys	C: 0.07	C: 0.04	184 (86.8)	99 (93.4)		1 (Reference)
Cys/Ser			27 (12.7)	6 (5.7)	0.14	0.39 (0.16-1.00)
Ser/Ser			1 (0.5)	1 (0.9)		1.77 (0.11-29.10)
Cys/Ser + Ser/Ser			28 (13.2)	7 (6.6)	0.08	0.44 (0.19-1.06)
ERCC6 rs4253211			211 (100)	102 (100)		
Arg/Arg	C: 0.11	C: 0.13	170 (80.6)	79 (77.5)		1 (Reference)
Arg/Pro			37 (17.5)	20 (19.6)	0.75	1.26 (0.68-2.33)
Pro/Pro			4 (1.9)	3 (2.9)		1.86 (0.39-8.91)
Arg/Pro + Pro/Pro			41 (19.4)	23 (22.5)	0.52	1.31 (0.72-2.37)
ERCC6 rs2228529			211 (100)	104 (100)		
Gln/Gln	G: 0.24	G: 0.20	118 (55.9)	66 (63.5)		1 (Reference)
Gln/Arg			86 (40.8)	35 (33.7)	0.44	0.67 (0.40-1.12)
Arg/Arg			7 (3.3)	3 (2.9)		0.72 (0.18-2.89)
Gln/Arg + Arg/Arg			93 (44.1)	38 (36.5)	0.20	0.67 (0.41-1.11)

Table III. Continued.

Genotype	MAF		Genotype frequency		P-value[a]	Adjusted OR (95% CI)[b]
	Controls	Cases	Controls, n (%)	Cases, n (%)		
XPC rs2228000			212 (100)	106 (100)		
Ala/Ala	T: 0.32	T: 0.30	95 (44.8)	47 (44.3)		1 (Reference)
Ala/Val			98 (46.2)	55 (51.9)	0.21	1.16 (0.71-1.88)
Val/Val			19 (9.0)	4 (3.8)		0.43 (0.14-1.37)
Ala/Val + Val/Val			117 (55.2)	59 (55.7)	0.94	1.04 (0.65-1.67)
XPC rs2228001			212 (100)	106 (100)		
Lys/Lys	C: 0.36	C: 0.41	82 (38.7)	39 (36.8)		1 (Reference)
Lys/Gln			108 (50.9)	47 (44.3)	0.10	0.96 (0.57-1.61)
Gln/Gln			22 (10.4)	20 (18.9)		1.93 (0.93-4.00)
Lys/Gln + Gln/Gln			130 (61.3)	67 (63.2)	0.74	1.12 (0.69-1.83)

[a]P-value determined by χ^2 test (cases vs. control group); [b]ORs were adjusted for gender (male and female), age (≤30, 31-49, 50-69, ≥70 years) and smoking status (non-smoker and smoker). [c]P<0.05. DTC, well-differentiated thyroid cancer; MAF, minor allele frequencies.

Through logistic regression analysis (Table III), we observed that the rs2230641 (*CCNH*) heterozygous genotype was significantly associated with increased DTC risk (adjusted OR=1.89, 95% CI=1.14-3.14, P=0.01). Similar results were verified when considering at least one variant allele (adjusted OR=1.79, 95% CI=1.09-2.93, P=0.02), further supporting an association between rs2230641 (*CCNH*) and DTC risk. Also, an almost significant association between the rs2227869 (*ERCC5*) heterozygous genotype and reduced DTC risk was observed (adjusted OR=0.39, 95% CI=0.16-1.00, P=0.05).

Following stratification according to histological criteria (Table IV), the DTC risk increase observed for rs2230641 (*CCNH*) remained in the follicular subset (adjusted OR=2.72, 95% CI=1.19-6.22, P=0.02, for heterozygous; adjusted OR=2.44, 95% CI=1.07-5.55, P=0.03, for variant allele carriers) and almost reached significance in the papillary subset (adjusted OR=1.74, 95% CI=0.99-3.07, P=0.05, for heterozygous; adjusted OR=1.69, 95% CI=0.98-2.92, P=0.06, for variant allele carriers), supporting the idea that this polymorphism may influence DTC susceptibility, irrespective of tumour type. The risk of papillary TC was significantly increased in rs2228001 (*XPC*) homozygous variant individuals (adjusted OR=2.33, 95% CI=1.05-5.16, P=0.04) and significantly reduced in rs2227869 (*ERCC5*) variant allele carriers (adjusted OR=0.25, 95% CI=0.07-0.86, P=0.03) and heterozygous individuals (adjusted OR=0.26, 95% CI=0.08-0.90, P=0.03). No significant differences in genotypic frequencies or adjusted ORs were observed for the remaining SNPs, either when considering overall DTC cases or its histological subsets, suggesting that these SNPs alone do not contribute to individual susceptibility to DTC.

To assess the effect of combined genotypes, further statistical analysis was applied to those SNPs that are located in the same gene (rs17655 and rs2227869 on *ERCC5*; rs4253211 and rs2228529 on *ERCC6*; rs2228000 and rs2228001 on *XPC*). Also, since SNPs in different NER genes may influence the way their expression products interact (hence, their repair activity), we also analyzed SNP-SNP interactions between different genes, as long as these interactions were biologically plausible. The genotype distribution of the rs17655/rs2227869 (*ERCC5*) combination was significantly different in cases and controls (P=0.01); however, no specific *ERCC5* genotype combination was associated with altered DTC risk (data not shown), probably due to the low number of patients included in each genetic subgroup. None of the remaining genotype combinations showed association with disease (data not shown).

Discussion

We conducted a hospital-based case-control study in a Caucasian Portuguese population to evaluate the potential modifying role of a comprehensive selection of 11 SNPs in 8 NER pathway genes in individual susceptibility to non-familial DTC. Overall, we observed that NER polymorphisms such as rs2230641 (*CCNH*) and, possibly, rs2227869 (*ERCC5*) and rs2228001 (*XPC*) were associated with DTC susceptibility. A consistent risk increase was observed for rs2230641 (*CCNH*) heterozygous and variant allele carriers, compared to wild-type individuals, both when considering all DTC cases and only the follicular subset. When considering only the papillary subset, the risk association almost reached significance for rs2230641 (*CCNH*) but was significant for the rs2228001 (*XPC*) variant genotype (increased risk). Also, a protective effect was observed for rs2227869 (*ERCC5*) in heterozygous and variant allele carriers, in the papillary subset. The association between the rs2227869 (*ERCC5*) heterozygous genotype and reduced DTC risk almost reached significance when all DTC cases were considered. No other significant correlation was observed for the remaining SNPs.

To our knowledge, this is the first study to assess the effect of these SNPs on DTC susceptibility. Our previous

Table IV. Genotype distribution in the case population (n=106) and associated DTC risk (adjusted ORs), after stratification according to histological type.

	Papillary carcinoma		Follicular carcinoma	
Genotype	n (%)	Adjusted OR (95% CI)[a]	n (%)	Adjusted OR (95% CI)[a]
CCNH rs2230641	78 (100)		28 (100)	
Val/Val	45 (57.7)	1 (Reference)	15 (53.6)	1 (Reference)
Val/Ala	30 (38.5)	1.74 (0.99-3.07)	13 (46.4)	**2.72 (1.19-6.22)[b]**
Ala/Ala	3 (3.8)	1.27 (0.32-5.15)	0 (0.0)	-
Val/Ala + Ala/Ala	33 (42.3)	1.69 (0.98-2.92)	13 (46.4)	**2.44 (1.07-5.55)[b]**
CDK7 rs2972388	75 (100)		26 (100)	
T/T	27 (36.0)	1 (Reference)	10 (38.5)	1 (Reference)
T/C	31 (41.3)	0.87 (0.47-1.60)	12 (46.2)	0.93 (0.37-2.31)
C/C	17 (22.7)	0.70 (0.35-1.43)	4 (15.4)	0.40 (0.12-1.37)
T/C + C/C	48 (64.0)	0.80 (0.46-1.40)	16 (61.5)	0.70 (0.30-1.65)
RAD23B rs1805329	78 (100)		28 (100)	
Ala/Ala	53 (67.9)	1 (Reference)	22 (78.6)	1 (Reference)
Ala/Val	22 (28.2)	1.06 (0.59-1.91)	5 (17.9)	0.56 (0.20-1.58)
Val/Val	3 (3.8)	1.27 (0.31-5.25)	1 (3.6)	1.26 (0.14-11.28)
Ala/Val + Val/Val	25 (32.1)	1.08 (0.61-1.90)	6 (21.4)	0.62 (0.24-1.63)
ERCC1 rs3212986	78 (100)		28 (100)	
C/C	49 (62.8)	1 (Reference)	15 (53.6)	1 (Reference)
C/A	27 (34.6)	0.72 (0.41-1.25)	12 (42.9)	1.07 (0.47-2.44)
A/A	2 (2.6)	0.46 (0.10-2.21)	1 (3.6)	0.76 (0.09-6.64)
C/A + A/A	29 (37.2)	0.69 (0.40-1.19)	13 (46.4)	1.04 (0.47-2.33)
ERCC4 rs1800067	75 (100)		27 (100)	
Arg/Arg	57 (76.0)	1 (Reference)	20 (74.1)	1 (Reference)
Arg/Gln	17 (22.7)	1.38 (0.71-2.66)	6 (22.2)	1.46 (0.54-3.99)
Gln/Gln	1 (1.3)	0.76 (0.08-7.20)	1 (3.7)	1.87 (0.18-19.10)
Arg/Gln + Gln/Gln	18 (24.0)	1.32 (0.69-2.50)	7 (25.9)	1.51 (0.59-3.88)
ERCC5 rs17655	77 (100)		28 (100)	
Asp/Asp	39 (50.6)	1 (Reference)	12 (42.9)	1 (Reference)
Asp/His	36 (46.8)	1.15 (0.67-1.96)	14 (50.0)	1.48 (0.64-3.43)
His/His	2 (2.6)	0.28 (0.06-1.27)	2 (7.1)	0.82 (0.17-4.03)
Asp/His + His/His	38 (49.4)	0.99 (0.59-1.68)	16 (57.1)	1.35 (0.60-3.05)
ERCC5 rs2227869	78 (100)		28 (100)	
Cys/Cys	75 (96.2)	1 (Reference)	24 (85.7)	1 (Reference)
Cys/Ser	3 (3.8)	**0.26 (0.08-0.90)[b]**	3 (10.7)	0.87 (0.24-3.15)
Ser/Ser	0 (0.0)	-	1 (3.6)	5.49 (0.32-95.50)
Cys/Ser + Ser/Ser	3 (3.8)	**0.25 (0.07-0.86)[b]**	4 (14.3)	1.09 (0.34-3.46)
ERCC6 rs4253211	76 (100)		26 (100)	
Arg/Arg	60 (78.9)	1 (Reference)	19 (73.1)	1 (Reference)
Arg/Pro	13 (17.1)	1.06 (0.52-2.15)	7 (26.9)	1.90 (0.71-5.07)
Pro/Pro	3 (3.9)	2.41 (0.50-11.72)	0 (0.0)	-
Arg/Pro + Pro/Pro	16 (21.1)	1.17 (0.60-2.28)	7 (26.9)	1.79 (0.67-4.78)
ERCC6 rs2228529	76 (100)		28 (100)	
Gln/Gln	47 (61.8)	1 (Reference)	19 (67.9)	1 (Reference)
Gln/Arg	26 (34.2)	0.71 (0.40-1.25)	9 (32.1)	0.64 (0.27-1.51)
Arg/Arg	3 (3.9)	0.95 (0.24-3.80)	0 (0.0)	-
Gln/Arg + Arg/Arg	29 (38.2)	0.73 (0.42-1.26)	9 (32.1)	0.58 (0.24-1.36)

Table IV. Continued.

Genotype	Papillary carcinoma		Follicular carcinoma	
	n (%)	Adjusted OR (95% CI)[a]	n (%)	Adjusted OR (95% CI)[a]
XPC rs2228000	78 (100)		28 (100)	
Ala/Ala	34 (43.6)	1 (Reference)	13 (46.4)	1 (Reference)
Ala/Val	43 (55.1)	1.23 (0.72-2.10)	12 (42.9)	0.92 (0.39-2.13)
Val/Val	1 (1.3)	0.15 (0.02-1.18)	3 (10.7)	1.30 (0.32-5.24)
Ala/Val + Val/Val	44 (56.4)	1.06 (0.63-1.80)	15 (53.6)	0.97 (0.44-2.16)
XPC rs2228001	78 (100)		28 (100)	
Lys/Lys	26 (33.3)	1 (Reference)	13 (46.4)	1 (Reference)
Lys/Gln	36 (46.2)	1.08 (0.60-1.95)	11 (39.3)	0.65 (0.27-1.54)
Gln/Gln	16 (20.5)	**2.33 (1.05-5.16)[b]**	4 (14.3)	1.17 (0.34-4.07)
Lys/Gln + Gln/Gln	52 (66.7)	1.28 (0.74-2.24)	15 (53.6)	0.73 (0.33-1.65)

[a]ORs were adjusted for gender (male and female), age (≤30, 31-49, 50-69, and ≥70 years), and smoking status (non-smoker and smoker). [b]P-value <0.05. DTC, well-differentiated thyroid cancer.

study reporting an association between an *ERCC2* haplotype (rs13181/rs1799793) and increased TC (mainly papillary) risk (17) is the only other association study that we are aware of, focusing on the role of NER pathway SNPs in TC susceptibility. However, studies correlating the polymorphisms considered in this study with cancer risk have been published for other types of cancer.

Concerning rs2230641 (*CCNH*), studies on oesophageal (22) bladder (23) and renal cell carcinoma (24) have yielded mostly negative results. Two significant associations have been reported, with opposite findings; according to Enjuanes *et al* (25), the minor allele is associated with decreased risk for chronic lymphocytic leukaemia; on the contrary, in line with our results, Chen *et al* (26), observed, in ever smokers, a significant association for the rs2230641 variant allele with bladder cancer risk and an almost 30-fold increased risk in carriers of the rs2230641 (*CCNH*), rs2228526 (*ERCC6*) and rs1805329 (*RAD23B*) variant alleles.

Previous evidence on the role of *XPC* polymorphisms on cancer risk is also conflicting; both rs2228001 and rs2228000 have been extensively investigated in case-control cancer association studies but, when considered separately, results are mostly negative, possibly due to insufficient sample size. Increasing the power through performance of meta-analysis has revealed small but significant increases in overall (27-29), bladder (27-31) and breast (29) cancer risk for rs2228000 and in overall (28,29), lung (27-30), bladder (29) and colorectal (29) cancer risk for rs2228001. Meta-analyses yielding negative results have also been published (32,33). The effect of *XPC* polymorphisms may be best represented by its haplotype since significantly increased cancer risk has been observed more frequently when considering both polymorphisms together, as a haplotype block (22,34), or in combined analysis with other NER variants (23,35,36).

With respect to rs2227869 (*ERCC5*), notably, results similar to our own have been reported by Hussain *et al* (37) in the only cancer association study we retrieved from our literature review; decreased stomach cancer risk was observed in heterozygous individuals, according to this study.

As for the remaining SNPs, rs3212986 (*ERCC1*), rs1800067 (*ERCC4*), rs17655 (*ERCC5*) and rs1805329 (*RAD23B*) have been extensively analyzed in prior cancer association studies, mostly with negative results. For rs3212986 (*ERCC1*), rs1800067 (*ERCC4*) and rs17655 (*ERCC5*) these findings are further corroborated by several meta-analyses that, in agreement with our report, demonstrated no clear association with overall (38-41), lung (42) or breast (43) cancer risk. rs2972388 (*CDK7*), rs4253211 and rs2228529 (*ERCC6*) have received little attention in the context of cancer susceptibility but the unique reports we found for each of these SNPs are substantially different from ours, as rs2972388 (*CDK7*) and rs2228529 (*ERCC6*) were associated, respectively, with increased breast cancer risk in a Korean population (44) and increased non-melanoma skin cancer risk in an American population (45). For rs4253211 (*ERCC6*), the variant allele seems to confer a protective effect towards laryngeal (36) and oesophageal (22) cancer, but no association with bladder cancer was observed (23).

CCNH codes for Cyclin H, a protein that, together with CDK7 and MAT1, forms the cyclin-activated kinase (CAK) complex. CAK integrates TFIIH, a larger complex implicated in DNA denaturation prior to damage excision. CAK can also phosphorylate nuclear receptors such as the retinoic acid or the estrogen receptors and a very different range of substrates (16). It is also involved in cell cycle regulation (46). Although data on the functional consequences of rs2230641 is lacking, the pleiotropic effects of CCNH on NER, cell cycle regulation and oestrogen receptor phosphorylation, among others, confer biological plausibility to our hypothesis that *CCNH* variants (namely, rs2230641) may be involved in cancer susceptibility. Its role in oestrogen receptor phosphorylation could be of particular significance for DTC, which, as previously noted, is

an endocrine tumour 3 times more prevalent in women than in men. Discrepancies with prior studies could therefore be explained on the basis of the specific hormonal involvement on DTC, insignificant for the types of cancer previously evaluated.

XPC codes for a DNA binding protein that, together with RAD23B and centrin 2, forms the distortion-sensing component of NER, thus playing a central role in the process of early damage recognition (16,47). XPC is also involved in DNA damage-induced cell cycle checkpoint regulation and apoptosis, removal of oxidative DNA damage and redox homeostasis (47,48). XPC deficiency has been correlated with decreased DNA repair capacity (48), and hypersensitivity to DNA-oxidizing agents such as X-rays (47), a well-known DTC risk factor, providing the rational basis for a putative involvement of *XPC* polymorphisms in DTC susceptibility. Notably, multinodular TC was recently reported as the most frequently observed internal tumour in Xeroderma pigmentosum type C patients (49), further substantiating the potential role of XPC in thyroid carcinogenesis. rs2228001 originates an aminoacid substitution in the interaction domain with TFIIH. *In silico* analysis indicates that rs2228001 may possibly be damaging and *in vitro* evidence demonstrates differential repair capacity [reviewed in reference (27)]. rs2228000 is located in the interaction domain of XPC with RAD23B and, although its functional significance remains unclear, it is predicted to be benign through *in silico* analysis (27). It is possible that both these variants, particularly their haplotypes, may alter NER capacity, thereby modulating cancer susceptibility. Despite the numerous case-control studies and meta-analyses that exist, clinical evidence is conflicting and, thus, further studies are warranted.

ERCC5 codes for an endonuclease that exerts its activity at the 3' side of the damaged strand (16). ERCC5 also plays a structural role, stabilizing the TFIIH complex; in its absence, the CAK complex and the ERCC2 subunit dissociate from the TFIIH core (50). Point mutations in *ERCC5* may give rise to Xeroderma pigmentosum and Cockayne syndrome, highlighting its importance for effective DNA repair.

It is possible that NER polymorphisms, through impairing oxidative DNA damage repair, may contribute to DTC development. In addition, it is possible that the pleiotropic actions of some NER proteins (such as CCNH or XPC, demonstrated to be involved in cell cycle regulation, apoptosis or hormone signalling), may convey these specific proteins a relevant role in carcinogenesis, particularly DTC.

Discrepancies from prior studies may have originated from the inherent characteristics of each cancer and respective organ. Divergent genetic background and environmental exposure of study populations may have also contributed. The low statistical power inherent to small sample use may explain some of our negative results. The histology-dependent differences observed for some SNPs could derive from different carcinogenesis pathways (hence, different genetic risk factors) among DTC histological types, as occurs between well-differentiated and anaplastic TC, or, more likely, from small sample size on stratified analysis.

Indeed, the main limitation of our study was sample size; small samples may be underpowered to detect modest effects of low penetrance genes and, on the other hand, may increase the probability that findings are attributable to chance, particularly after stratification (small numbers in the subgroups). The success of more sophisticated statistical analysis, such as haplotype analysis and evaluation of gene-gene and gene-environment interactions, is also limited. Moreover, we cannot exclude the possibility that other variants in linkage disequilibrium with the ones considered here could be responsible for the observed associations.

In conclusion, our study provides, for the first time, insight into the potential role of *CCNH*, *ERCC5*, *XPC* and other NER polymorphisms in DTC susceptibility. Additional studies with larger sample sizes are necessary to validate our findings and to provide conclusive evidence for associations between these and other NER variants and DTC risk. Such studies should be powered to allow for haplotype analysis and evaluation of gene-gene and gene-environment interactions. Functional studies are also warranted, as well as a broader analysis of the involvement of NER variants in DTC progression and therapy response.

Acknowledgements

This study was supported by the Projects PTDC/SAu-OSM/105572/2008 and PTDC/SAu-ESA/102367/2008, Projecto Estratégico Nº Pest-E/SAU/UI0009/2011 from Fundação para a Ciência e Tecnologia (FCT).

References

1. Grubbs EG, Rich TA, Li G, *et al*: Recent advances in thyroid cancer. Curr Probl Surg 45: 156-250, 2008.
2. Dal Maso L, Bosetti C, La Vecchia C and Franceschi S: Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control 20: 75-86, 2009.
3. Adjadj E, Schlumberger M and de Vathaire F: Germ-line DNA polymorphisms and susceptibility to differentiated thyroid cancer. Lancet Oncol 10: 181-190, 2009.
4. Gudmundsson J, Sulem P, Gudbjartsson DF, *et al*: Common variants on 9q22.33 and 14q13.3 predispose to thyroid cancer in European populations. Nat Genet 41: 460-464, 2009.
5. Sigurdson AJ, Hauptmann M, Alexander BH, Doody MM, Thomas CB, Struewing JP and Jones IM: DNA damage among thyroid cancer and multiple cancer cases, controls, and long-lived individuals. Mutat Res 586: 173-188, 2005.
6. Hoeijmakers JH: Genome maintenance mechanisms for preventing cancer. Nature 411: 366-374, 2001.
7. Ho T, Li G, Lu J, Zhao C, Wei Q and Sturgis EM: Association of *XRCC1* polymorphisms and risk of differentiated thyroid carcinoma: a case-control analysis. Thyroid 19: 129-135, 2009.
8. Chiang FY, Wu CW, Hsiao PJ, *et al*: Association between polymorphisms in DNA base excision repair genes *XRCC1*, *APE1*, and *ADPRT* and differentiated thyroid carcinoma. Clin Cancer Res 14: 5919-5924, 2008.
9. Akulevich NM, Saenko VA, Rogounovitch TI, *et al*: Polymorphisms of DNA damage response genes in radiation-related and sporadic papillary thyroid carcinoma. Endocr Relat Cancer 16: 491-503, 2009.
10. Santos LS, Branco SC, Silva SN, *et al*: Polymorphisms in base excision repair genes and thyroid cancer risk. Oncol Rep 28: 1859-1868, 2012.
11. Gomes BC, Silva SN, Azevedo AP, *et al*: The role of common variants of non-homologous end-joining repair genes *XRCC4*, *LIG4* and *Ku80* in thyroid cancer risk. Oncol Rep 24: 1079-1085, 2010.
12. Xu L, Doan PC, Wei Q, Liu Y, Li G and Sturgis EM: Association of *BRCA1* functional single nucleotide polymorphisms with risk of differentiated thyroid carcinoma. Thyroid 22: 35-43, 2012.
13. Bastos HN, Antão MR, Silva SN, *et al*: Association of polymorphisms in genes of the homologous recombination DNA repair pathway and thyroid cancer risk. Thyroid 19: 1067-1075, 2009.

14. Gatzidou E, Michailidi C, Tseleni-Balafouta S and Theocharis S: An epitome of DNA repair related genes and mechanisms in thyroid carcinoma. Cancer Lett 290: 139-147, 2010.
15. Silva SN, Gomes BC, Rueff J and Gaspar JF: DNA repair perspectives in thyroid and breast cancer: the role of DNA repair polymorphisms. In: DNA Repair and Human Health. Vengrova S (ed). InTech, pp459-484, 2011.
16. Nouspikel T: DNA repair in mammalian cells: nucleotide excision repair: variations on versatility. Cell Mol Life Sci 66: 994-1009, 2009.
17. Silva SN, Gil OM, Oliveira VC, *et al*: Association of polymorphisms in *ERCC2* gene with non-familial thyroid cancer risk. Cancer Epidemiol Biomarkers Prev 14: 2407-2412, 2005.
18. Zhao H, Wang LE, Li D, Chamberlain RM, Sturgis EM and Wei Q: Genotypes and haplotypes of *ERCC1* and *ERCC2/XPD* genes predict levels of benzo[α]pyrene diol epoxide-induced DNA adducts in cultured primary lymphocytes from healthy individuals: a genotype-phenotype correlation analysis. Carcinogenesis 29: 1560-1566, 2008.
19. Yu T, Liu Y, Lu X, *et al*: Excision repair of BPDE-adducts in human lymphocytes: diminished capacity associated with ERCC1 C8092A (rs3212986) polymorphism. Arch Toxicol 87: 699-709, 2013.
20. Pingarilho M, Oliveira NG, Martins C, Fernandes AS, de Lima JP, Rueff J and Gaspar JF: Genetic polymorphisms in detoxification and DNA repair genes and susceptibility to glycidamide-induced DNA damage. J Toxicol Environ Health A 75: 920-933, 2012.
21. Lange K, Cantor R, Horvath S, Perola M, Sabatti C, Sinsheimer J and Sobel E: Mendel version 4.0: a complete package for the exact genetic analysis of discrete traits in pedigree and population data sets. Am J Hum Genet 69: A1886, 2001.
22. Pan J, Lin J, Izzo JG, *et al*: Genetic susceptibility to esophageal cancer: the role of the nucleotide excision repair pathway. Carcinogenesis 30: 785-792, 2009.
23. Wu X, Gu J, Grossman HB, *et al*: Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. Am J Hum Genet 78: 464-479, 2006.
24. Lin J, Pu X, Wang W, Matin S, Tannir NM, Wood CG and Wu X: Case-control analysis of nucleotide excision repair pathway and the risk of renal cell carcinoma. Carcinogenesis 29: 2112-2119, 2008.
25. Enjuanes A, Benavente Y, Bosch F, *et al*: Genetic variants in apoptosis and immunoregulation-related genes are associated with risk of chronic lymphocytic leukemia. Cancer Res 68: 10178-10186, 2008.
26. Chen M, Kamat AM, Huang M, *et al*: High-order interactions among genetic polymorphisms in nucleotide excision repair pathway genes and smoking in modulating bladder cancer risk. Carcinogenesis 28: 2160-2165, 2007.
27. Francisco G, Menezes PR, Eluf-Neto J and Chammas R: XPC polymorphisms play a role in tissue-specific carcinogenesis: a meta-analysis. Eur J Hum Genet 16: 724-734, 2008.
28. Qiu L, Wang Z, Shi X and Wang Z: Associations between XPC polymorphisms and risk of cancers: a meta-analysis. Eur J Cancer 44: 2241-2253, 2008.
29. He J, Shi TY, Zhu ML, Wang MY, Li QX and Wei QY: Associations of Lys939Gln and Ala499Val polymorphisms of the *XPC* gene with cancer susceptibility: a meta-analysis. Int J Cancer: Feb 7, 2013 (Epub ahead of print). doi: 10.1002/ijc.28089.
30. Zhang D, Chen C, Fu X, *et al*: A meta-analysis of DNA repair gene *XPC* polymorphisms and cancer risk. J Hum Genet 53: 18-33, 2008.
31. Stern MC, Lin J, Figueroa JD, *et al*: Polymorphisms in DNA repair genes, smoking, and bladder cancer risk: findings from the international consortium of bladder cancer. Cancer Res 69: 6857-6864, 2009.
32. Zheng W, Cong XF, Cai WH, Yang S, Mao C and Zou HW: Current evidences on XPC polymorphisms and breast cancer susceptibility: a meta-analysis. Breast Cancer Res Treat 128: 811-815, 2011.
33. Liu C, Yin Q, Hu J, Li L, Zhang Y and Wang Y: A meta-analysis of evidences on XPC polymorphisms and lung cancer susceptibility. Tumor Biol 34: 1205-1213, 2013.
34. D'Amelio AM, Monroy C, El-Zein R and Etzel CJ: Using haplotype analysis to elucidate significant associations between genes and Hodgkin lymphoma. Leuk Res 36: 1359-1364, 2012.
35. Bai Y, Xu L, Yang X, *et al*: Sequence variations in DNA repair gene *XPC* is associated with lung cancer risk in a Chinese population: a case-control study. BMC Cancer 7: 81, 2007.
36. Abbasi R, Ramroth H, Becher H, Dietz A, Schmezer P and Popanda O: Laryngeal cancer risk associated with smoking and alcohol consumption is modified by genetic polymorphisms in *ERCC5*, *ERCC6* and *RAD23B* but not by polymorphisms in five other nucleotide excision repair genes. Int J Cancer 125: 1431-1439, 2009.
37. Hussain SK, Mu LN, Cai L, *et al*: Genetic variation in immune regulation and DNA repair pathways and stomach cancer in China. Cancer Epidemiol Biomarkers Prev 18: 2304-2309, 2009.
38. Li Y, Gu S, Wu Q, *et al*: No association of *ERCC1* C8092A and T19007C polymorphisms to cancer risk: a meta-analysis. Eur J Hum Genet 15: 967-973, 2007.
39. Shi TY, He J, Qiu LX, *et al*: Association between *XPF* polymorphisms and cancer risk: a meta-analysis. PLoS One 7: e38606, 2012.
40. Zhang L, Wang J, Xu L, *et al*: Nucleotide excision repair gene *ERCC1* polymorphisms contribute to cancer susceptibility: a meta-analysis. Mutagenesis 27: 67-76, 2012.
41. Zhu ML, Wang M, Cao ZG, *et al*: Association between the *ERCC5* Asp1104His polymorphism and cancer risk: a meta-analysis. PLoS One 7: e36293, 2012.
42. Hung RJ, Christiani DC, Risch A, *et al*: International Lung Cancer Consortium: pooled analysis of sequence variants in DNA repair and cell cycle pathways. Cancer Epidemiol Biomarkers Prev 17: 3081-3089, 2008.
43. Ding DP, He XF and Zhang Y: Lack of association between XPG Asp1104His and XPF Arg415Gln polymorphism and breast cancer risk: a meta-analysis of case-control studies. Breast Cancer Res Treat 129: 203-209, 2011.
44. Jeon S, Choi JY, Lee KM, *et al*: Combined genetic effect of *CDK7* and *ESR1* polymorphisms on breast cancer. Breast Cancer Res Treat 121: 737-742, 2010.
45. Wheless L, Kistner-Griffin E, Jorgensen TJ, *et al*: A community-based study of nucleotide excision repair polymorphisms in relation to the risk of non-melanoma skin cancer. J Invest Dermatol 132: 1354-1362, 2012.
46. Lolli G and Johnson LN: CAK-cyclin-dependent activating kinase: a key kinase in cell cycle control and a target for drugs? Cell Cycle 4: 572-577, 2005.
47. Melis JP, Luijten M, Mullenders LH and van Steeg H: The role of XPC: implications in cancer and oxidative DNA damage. Mutat Res 728: 107-117, 2011.
48. Chen Z, Yang J, Wang G, Song B, Li J and Xu Z: Attenuated expression of xeroderma pigmentosum group C is associated with critical events in human bladder cancer carcinogenesis and progression. Cancer Res 67: 4578-4585, 2007.
49. Hadj-Rabia S, Oriot D, Soufir N, *et al*: Unexpected extradermatological findings in 31 patients with xeroderma pigmentosum type C. Br J Dermatol 168: 1109-1113, 2013.
50. Ito S, Kuraoka I, Chymkowitch P, *et al*: XPG stabilizes TFIIH, allowing transactivation of nuclear receptors: implications for Cockayne syndrome in XP-G/CS patients. Mol Cell 26: 231-243, 2007.