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Association study of genetic variation in DNA repair pathway genes and risk of basal cell carcinoma

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Abstract

DNA repair plays a critical role in protecting the genome from ultraviolet radiation and maintaining the genomic integrity of cells. Genetic variants in DNA repair-related genes can influence an individual's DNA repair capacity, which may be related to the risk of developing basal cell carcinoma (BCC). We comprehensively assessed the associations of 2,965 independent single-nucleotide polymorphisms (SNPs) across 165 DNA repair pathway genes with BCC risk in a genome-wide association meta-analysis totaling 17,187 BCC cases and 287,054 controls from two data sets. After multiple testing corrections, we identified three SNPs (rs2805831 upstream of *XPA*: OR = 0.93, $P = 1.35 \times 10^{-6}$; rs659857 in exon of *MUS81*: OR = 1.06, $P = 3.09 \times 10^{-6}$; and rs57343616 in 3' UTR of *NABP2*: OR = 1.11, $P = 6.47 \times 10^{-6}$) as significantly associated with BCC risk in meta-analysis, and all of them were nominally significant in both data sets. Furthermore, rs659857 [T] was significantly associated with decreased expression of *MUS81* mRNA in the expression quantitative trait locus (eQTL) analysis. Our findings suggest that the inherited common variation in three DNA repair genes-*XPA*, *MUS81* and *NABP2*-may be involved in the development of BCC. To our knowledge, our study is the first report thoroughly examining the effects of SNPs across DNA repair pathway genes on BCC risk based on a genome-wide association meta-analysis.

Keywords

basal cell carcinoma; DNA repair pathway genes; genome-wide association meta-analysis; single nucleotide polymorphism

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Introduction

Skin cancer is the most frequent malignancy among Caucasians in the United States¹ as well as other countries.² Current estimates are that one in five Americans will develop skin cancer during his or her lifetime.³ Basal cell carcinoma (BCC), a basal keratinocyte tumor in the epidermis, accounts for 80–90% of all primary skin cancers.⁴ In the USA, more than one million BCC cases are diagnosed each year.⁵ Although BCCs are slow-growing, locally invasive tumors, they can lead to extensive morbidity through recurrence and tissue destruction, imposing a growing burden on healthcare services.

Ultraviolet (UV) radiation is generally accepted as the most important environmental risk factor for BCC, causing cellular DNA damage by inducing the formation of DNA photoproducts, bulky monoadducts, crosslinks, and oxidative damage.^{6–7} One essential defense mechanism against skin cancer is the ability to repair DNA damage induced by UV light. DNA repair pathway genes form a complex network that continuously monitors chromosomes to correct damaged nucleotide residues generated by exposure to carcinogens and cytotoxic compounds.⁸ Toxic and mutagenic consequences are minimized by discrete DNA repair pathways such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end-joining (NHEJ).⁸ Reduced capacity for DNA repair after UV light-induced DNA damage has been established as an independent risk factor for BCC development.⁹ The importance of NER in the etiology of skin cancer has been clearly illustrated. It is the main process responsible for repairing DNA photoproducts, which is generated upon the direct absorption of UVB (280–320 nm).¹⁰ However, studies have shown that UVA (320–400 nm) predominantly present in sunlight, induces oxidative DNA damage, which further lead to double-strand breaks (DSBs).^{11, 12} This process may also contribute to the development of non-melanoma skin cancer.¹³ Homologous recombination (HR) and non-homologous end-joining (NHEJ) are two distinct mechanisms in the repair of DSBs in mammalian cells. Therefore, their repair capacity may influence individual's risk of UV induced skin cancer.¹³

Genetic variation in DNA repair-related genes can modulate DNA repair capacity^{14,15} and may further affect BCC susceptibility. A number of studies have examined the associations between polymorphisms in DNA repair genes and BCC risk, with inconsistent findings.^{13, 16–20} However, many of these studies focused on only a few genes and only functional single nucleotide polymorphisms (SNPs), that is, instances in which variation in a single base pair in the DNA results in a different amino acid upon translation. As the number of human DNA repair pathway genes identified has risen to as many as 165,⁸ a more complete and systematic evaluation of DNA repair gene variation in relation to BCC is now called for. In addition, the function of 'silent' polymorphisms under different mechanisms has been shown, such as epigenetic regulation of promoters,²¹ pre-transcriptional regulation via miRNA targeting of 3' untranslated regions,²² and post-translational modification via synonymous polymorphisms in exons.²³ Including markers from each of these regions is advantageous for identifying new BCC susceptibility-related variants. Therefore, in the present study, we thoroughly examine the effects of common genetic variation across DNA repair-related pathway genes on BCC risk by extracting genotyping data on 165 related genes from a genome-wide association meta-analysis.

Materials and methods

Study population

This study was based on a genome-wide association meta-analysis of BCC consisting of two GWAS datasets - the BCC case-control study within 23andMe research and the BCC case-control study within the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). A total of 17,187 cases and 287,054 controls of European ancestry were included. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The first GWAS set comprised 12,945 self-reported BCC cases and 274,252 controls among 23andMe research participants, who were described in a previous study.²⁴ Briefly, 23andMe gathers genetic information by genotyping sample material provided by its customers; phenotypic information is collected via customer responses to online surveys. All information came from 23andMe research participants who provided informed consent to take part in this research, in accord with 23andMe's human subjects protocol (reviewed and approved by Ethical and Independent Review Services, a AAHRPP-accredited IRB). Validation assessment with adjudicated medical records demonstrated a high validity of self-reported diagnosis with sensitivity and specificity of 93% and 99%, respectively. The second GWAS consisted of 4,242 self-reported BCC cases and 12,802 controls from the NHS and the HPFS, whose participants were described in a previous study.²⁴ The NHS consists of 121,700 female registered nurses between the ages of 30 and 55 years at enrollment. They returned the initial self-administered questionnaire in 1976 and then completed questionnaires biennially. Blood samples were collected from 32,826 participants. Information on BCC development was first collected in the 1984 questionnaire. For the HPFS, in 1986, 51,529 men in health professions aged 40–75 years answered a detailed mailed questionnaire, and 18,159 participants provided blood samples. Updated information was obtained by questionnaire every two years. Information on BCC development was first collected in the 1986 questionnaire. The protocol was approved by the Institutional Review Board at Brigham and Women's Hospital and the Harvard School of Public Health. All of the participants provided informed consent.

Two genome-wide association analyses and meta-analyses

Association analysis for 23andMe research was performed using unconditional logistic regression, assuming an additive model with adjustment for age, sex, and population stratification, generating the following model: $BCC\ diagnosis \sim age + sex + pc.0 + pc.1 + pc.2 + pc.3 + pc.4 + genotype$. Further information on the analysis was provided previously.²⁴ The association analysis for Harvard GWAS was also described in a previous study.²⁴ In brief, association analysis was performed using unconditional logistic regression under an additive model with adjustment for age, sex, and the first five principal components, generating the following model: $BCC\ diagnosis \sim age + sex + pc.1 + pc.2 + pc.3 + pc.4 + pc.5 + genotype$. After the imputation process was conducted in two datasets separately, we had 12,725,604 SNPs in the 23andMe dataset and 8,557,099 SNPs in the Harvard dataset. A total of 8,262,448 SNPs available in both datasets were included in further meta-analysis. Betas from the two GWAS studies were combined by a meta-analysis, with weights

proportional to the inverse variance of the beta in each study. Heterogeneity of per-SNP effect sizes in studies contributing to each GWAS and the overall meta-analysis was assessed by the Q test and the I^2 index, and fixed effects meta-analysis was conducted. A total of 8,262,448 SNPs in both datasets were included in further analysis.

DNA repair genes and SNPs selection

We selected human DNA repair pathway genes according to a review article.⁸ A complete list of these genes can be found on http://sciencepark.mdanderson.org/labs/wood/DNA_Repair_Genes.html. These pathways/genes are provided in Supplementary Table S1. SNPs within the 165 DNA repair-related genes and their ± 50 kb flanking regions were extracted for further analysis.

Exposure data collection

In the Harvard cohort, information regarding skin cancer risk factors was obtained from the retrospective supplementary questionnaire. Information on history of residence (states and towns) was collected, and 11 states of residence of cohort members at baseline were grouped into three regions: Northeast (Connecticut, Massachusetts, Maryland, New Jersey, New York, and Pennsylvania), North Central (Michigan and Ohio), and West and South (California, Texas, and Florida). To estimate sunlight exposure for each subject, a UV database for all 50 U.S. states was developed using reports from the Climatic Atlas of the United States, which reports mean daily solar radiation (in Langley) at the earth's surface for weather stations around the country (National Oceanic and Atmospheric Administration; 1983). Records of average annual solar radiation for January and July were extracted to represent winter and summer radiation, respectively. The mean solar radiation for each individual's past (at different age categories) and current residence was derived from the UV values measured at the nearest weather station, and both summer and winter radiation indices were developed for each residence. We also developed a cumulative lifetime sun exposure by combining the UV database and the information obtained from the supplementary questionnaires.

Statistical analysis

We used an online analysis tool - SNP Effect Concordance Analysis (SECA; <http://neurogenetics.qimrberghofer.edu.au/SECA/>) - to remove SNPs in linkage disequilibrium (LD) ($r^2 > 0.1$) within 10 Mb and kept a set of independent SNPs with the lowest P values in overall meta-analysis. Among these independent SNPs, we further selected those that reached nominal significance level of $P < 0.05$ in both GWAS datasets with consistent direction of association as index SNPs. We performed eQTL analysis using the Genotype-Tissue Expression (GTEx) Portal (<http://www.gtexportal.org/home/>). Genotype data from 1000G Phase 3 CEU (b37 rsIDs) was used for LD estimation. To evaluate interactions between sun exposure and genotypes, we modeled sun exposure level as a continuous variable using the median value among controls for each tertile in the Harvard cohort, which allowed us to assess the statistical significance of interaction by likelihood ratio tests. We also constructed a multivariable confounder score to summarize pigment traits in the Harvard cohort.²⁵ Briefly, we applied the logistic regression coefficients from a multivariable model for skin cancer risk, including age, gender, natural hair color, times of

blistered sunburn and tendency to sunburn during adolescence, to each individual's values for the latter three of these variables and summed the values to compute a pigment score in the logit scale. We used the median value for this score among controls to identify participants with low, intermediate, and high pigmentation. All statistical tests were two-sided.

Results

The distribution of cases and controls according to gender and age is provided in Table 1. In the overall meta-analysis of two GWAS datasets totaling 17,187 cases and 287,054 controls, we extracted 59,559 SNPs across the 165 DNA repair-related genes and within their ± 50 kb flanking regions. After removing SNPs in LD ($r^2 > 0.1$), 2,965 independent SNPs remained (**Materials and methods**). We found 14 SNPs significantly associated with BCC risk after performing multiple testing corrections with the Bonferroni single-step method (corrected α : $0.05/2,965 = 1.69 \times 10^{-5}$). Among them, eight SNPs reached a nominal significance level of $P < 0.05$ in both GWAS datasets with a consistent direction of association. These eight SNPs are across or within ± 50 -kb flanking regions of five different DNA repair genes - *XPA* rs2805831, *MUS81* rs659857, *NABP2* (also known as *SSBI*) rs57343616, *FANCA* rs149705807 rs9933498 rs12931267 rs17232309, and *TP53* rs35850753.

Among the five DNA repair pathway genes, three - *XPA* rs2805831 (NER), *MUS81* rs659857 (HR), and *NABP2* rs57343616 (with known DNA repair function) - were identified for the first time as related to BCC susceptibility (Table 2). Their minor allele frequency (MAF), imputation quality, and effect heterogeneity statistics are provided in Supplementary Table S2. *FANCA* is located 180 kb from the *MC1R* gene, a well-known critical pigmentation gene consistently associated with BCC risk.⁵ We evaluated the effect of one BCC-susceptibility SNP (rs1805007) in the *MC1R* gene on the association between *FANCA* and BCC risk. After adjusting for this SNP, the *FANCA* variants were no longer associated with BCC risk. This suggested that the *FANCA* signals we detected in the present study are explained by the *MC1R* variants nearby. *TP53* rs35850753 is in strong LD with rs78378222 ($r^2 = 0.82$), which was demonstrated to be significantly associated with BCC risk in a previous GWAS.²⁵ The data of the other five BCC susceptibility SNPs located in previously reported loci were shown in Supplementary Table S3.

Furthermore, we performed expression quantitative trait locus (eQTL) analysis using GTEx Portal, and found that the risk allele (T) of rs659857 was significantly associated with decreased expression of *MUS81* mRNA in 338 whole blood samples ($P = 0.018$), while no eQTL effects were identified for the other two index SNPs.

We evaluated potential gene-environment interactions between our index polymorphisms and cumulative sun exposure among the pooled population in the Harvard dataset. No statistically significant interactions were identified (P values for interaction tests > 0.05). We further conducted interaction analyses between polymorphisms and pigment score created in the Harvard dataset, and again no significant interactions were identified (P values for interaction tests > 0.05). When stratified by sun exposure level (low, intermediate, or high) and pigment score (low, intermediate, or high) among the pooled population in the Harvard

dataset, we did not find any significant difference of effect sizes in subgroups (all P values for heterogeneity > 0.05).

Because the association of the three SNPs with BCC risk may also be mediated by LD with other potential causal loci, we conducted pair-wise LD analysis in distinct gene regions. Some polymorphisms in LD ($r^2 > 0.1$) with the three index SNPs also exhibited significant associations with BCC risk ($P < 1.69 \times 10^{-5}$), but none showed stronger effect than the index SNPs (Supplementary Table S4).

Discussion

In view of the plethora of types of lesions, no single repair process can cope with all varieties of damage. Instead, numerous DNA repair pathways form a complex network that protects the genome's integrity from exogenous (radiation, chemicals, drugs) and endogenous (free radicals) damage.⁸ Their biological importance is demonstrated by the existence of dramatic diseases caused by a deficiency in one of these pathways.¹⁰ Because of the importance of maintaining genomic integrity in the general and specialized functions of cells, genes coding for DNA repair molecules have been proposed as candidate genes for skin cancer susceptibility. There are some published data on select genetic polymorphisms in DNA repair genes and BCC risk, but the findings are not consistent. In our present candidate gene analysis based on a large GWAS meta-analysis, we found evidence that common variants in *XPA*, *MUS81*, and *NABP2* genes are significantly associated with BCC risk.

rs2805831 at 9q22.33 resides 7 kb upstream of the *XPA* gene, which is a necessary component of the NER pathway. NER is a versatile repair system responsible for removing a wide variety of bulky, helix-distorting lesions that interfere with base pairing and generally obstruct transcription and normal replication.¹⁰ NER's importance in the etiology of skin cancer is clearly illustrated by classical xeroderma pigmentosum (XP), a heterogeneous genetic disorder in which rare, highly penetrant mutations disrupt NER's ability to remove DNA photoproducts. XP is caused by mutations in one of eight genes (XP complementation groups A-G), and patients exhibit extremely high sensitivity to UV radiation and have a more than 1,000-fold increased risk of skin cancers.^{27,28} It thus stands to reason that more common but less penetrant NER gene variants may be associated with BCC risk in the general population. It has been demonstrated that null mutations in the *XPA* gene lead to the most severe form of XP.²⁹ The index SNP *XPA* rs2805831 is in LD with rs1800975 ($r^2 = 0.106$, $D' = 1.000$), which have been associated with various cancers. We observed that in our study, the association of rs1800975 with BCC in the two GWAS data sets was inconsistent and it was not statistically significant after multiple testing corrections in the meta-analysis. Miller *et al.* have associated rs1800975 [T] allele with decreased risk of BCC and SCC in a previous study with small sample size (886 BCC cases, 682 SCC cases vs. 796 controls), and the association was marginally significant ($P = 0.03$ for BCC and $P = 0.05$ for SCC).¹⁹ However, it was reported that [T] allele was significantly associated with increased risk of some other cancers like lung cancer, breast cancer, gastric cardiac adenocarcinoma and oral premalignant lesions.^{30–33} In our data, [T] allele was associated with elevated BCC risk, but the association was not significant. The association of *XPA* with skin cancer may be driven by other markers, including rs2805831 that we reported in the present study.

Another index SNP rs659857 is a synonymous variant and also an eQTL of *MUS81* in whole blood. We found that the rs659857 risk allele (T) was associated with decreased expression of *MUS81* mRNA. *MUS81* is an important gene involved in the HR, which is responsible for repairing DSBs in mammalian cells. According to previous studies, UVA-induced oxidative DNA damage and DNA replication blockage by UVB-induced photoproducts can lead to DSBs.¹³ To our knowledge, biological evidence on the involvement of DSBs in non-melanoma skin cancer is weak. Recent work has connected β -human papillomavirus genus (β -HPVs) to non-melanoma skin cancers.³⁴ Wallace *et al.* further explored the underlying mechanism and found that β -HPVs act as co-factors that enhance the mutagenic capacity of UV-exposure by disrupting the repair of DSBs.³⁵ In addition, genetic polymorphisms in DSB repair genes like *XRCC2* and *XRCC3* have been demonstrated to confer predispositions to UV-induced skin cancer.¹³ Therefore, it is biological plausible that DSBs are involved in the development of UV-induced skin cancer and impairment of DSBs repair process could increase risk of skin cancer. SNPs in human *MUS81* that reduce protein activity have been proposed as breast cancer susceptibility factors.³⁶ Moreover, reduced *MUS81* expression has been observed in human carcinomas, including gastric carcinoma, colon carcinoma, and hepatocellular carcinoma.^{37–39} Our data suggest that common variation in *MUS81* plays a role in the development of BCC.

The third index SNP, rs57343616, is located in the 3' untranslated region (UTR) of the *NABP2* gene, which has been associated with DNA repair. NABP2, also known as hSSB1, is one of the single-stranded DNA (ssDNA)-binding proteins (SSBs), which are ubiquitous and essential for a variety of DNA metabolic processes, including replication, recombination, damage detection, and repair.⁴⁰ Previous studies verified the importance of NABP2 in the repair of DNA double-strand breaks via homologous recombination and in the maintenance and repair of DNA replication forks.^{41,42} New evidence proved that NABP2 is also indispensable following oxidative damage. Cells lacking NABP2 are sensitive to oxidizing agents, have deficient ATM and p53 activation, and cannot effectively repair the oxidation of DNA by reactive oxygen species (ROS).⁴³ The present study provides the first evidence for an association between *NABP2* gene variation and skin cancer risk.

Based on a large genome-wide association meta-analysis, we identified three novel BCC susceptibility loci with roles in DNA repair. To our knowledge, this is the most comprehensive evaluation of common inherited variation in candidate DNA-damage repair pathway genes in relation to BCC risk. Some potential limitations of our study also merit discussion. First, the present study included only unrelated U.S. Caucasians, which lacked racial and geographic diversity. We need future studies in other populations from different ethnic backgrounds or geographical areas to confirm our findings and their generalizability. Second, age and gender were not perfectly matched between cases and controls in this study. However, it is very common for GWAS studies to use controls that are not matched for demographic factors.^{44–47} Notably, age for the most part is not a confounder in SNP association tests. In the present study, we included age, gender, and genetic principal components in our regressions as covariates. This kind of study design with the participants from the Harvard and 23andMe cohorts have been used in many other GWAS studies.^{24, 48, 49} In sum, our findings suggest that the inherited common variation in *XPA*, *MUS81*,

and *NABP2* may be involved in the development of BCC. Further work is warranted on the functional characterization of index and linked SNPs in these regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

Genetic variations in DNA repair pathway genes may influence BCC susceptibility. Here, single nucleotide polymorphisms (SNPs) across 165 DNA repair pathway genes were examined for associations with BCC risk. Three new BCC susceptibility loci were identified, and additional BCC risk variants were located within two previously reported regions. The findings warrant further study of the relevance to BCC development of three DNA repair genes- *XPA*, *MUS81* and *NABP2*.

Table 1

Gender and age of BCC cases and controls from each GWAS.

	Status	n (%)	Male (%)	Age < 30 yr	Age 30–45	Age 46–60	Age > 60
23andMe (n = 287,197)	Cases	12945 (4.5)	6700 (52)	42 (0.3)	650 (5)	3194 (25)	9059 (70)
	Controls	274252 (95.5)	148415 (54)	39673 (14)	83162 (30)	74977 (27)	76440 (28)
Harvard (n = 12,343)	Cases	1777 (24.7)	834 (46.9)	5 (0.3)	500 (28.1)	978 (55.0)	294 (16.5)
	Controls	5411 (75.3)	2385 (44.1)	43 (0.8)	2068 (38.2)	2533 (46.8)	767 (14.2)
<i>Illumina</i>	Cases	1268 (25.6)	368 (29.0)	6 (0.5)	472 (37.2)	678 (53.5)	112 (8.8)
	Controls	3685 (74.4)	1029 (27.9)	33 (0.9)	1681 (45.6)	1692 (45.9)	279 (7.6)
<i>Omni</i>	Cases	1197 (24.4)	102 (42.9)	0 (0.0)	72 (30.2)	137 (57.6)	29 (12.2)
	Controls	3706 (75.6)	1238 (33.4)	34 (0.9)	1671 (45.1)	1651 (44.5)	350 (9.4)
All Harvard	Cases	4242 (24.9)	1649 (38.9)	15 (0.4)	1375 (32.4)	2301 (54.2)	551 (13.0)
	Controls	12802 (75.1)	4652 (36.3)	110 (0.9)	5420 (42.3)	5876 (45.9)	1396 (10.9)
Combined meta-analysis (n = 299,480)	Cases	17187 (5.6)	8349 (49)	57 (0.3)	2025 (12)	5495 (32)	9610 (56)
	Controls	287054 (94.4)	153067 (53)	39783 (14)	88582 (31)	80853 (28)	77836 (27)

Counts and percentages for cases and controls (n (%)) of two GWASs data sets are listed above. We also report number and percentage of male subjects, subjects with age < 30 years, subjects with age 30–45 years, subjects with age 46–60 years, and subjects with age > 60 years. Harvard data set is further subdivided based on platform used for genotyping.

Table 2

Three novel independent SNPs significantly associated with BCC risk in both GWAS studies and the meta-analysis.

SNP	Region	DNA repair gene	Major/minor	MAF	Meta-analysis		23andMe		Harvard		P_{het}	I^2
					OR	P	OR	P	OR	P		
rs2805831	9q22.33	<i>XPA</i>	G/A	0.17	0.93	1.35×10^{-6}	0.93	3.00×10^{-5}	0.92	1.22×10^{-2}	0.75	0.0%
rs659857	11q13.1	<i>MUS81</i>	C/T	0.33	1.06	3.09×10^{-6}	1.06	2.35×10^{-5}	1.05	5.00×10^{-2}	0.83	0.0%
rs7343616	12q13.3	<i>NABP2</i>	C/T	0.07	1.11	6.47×10^{-6}	1.11	1.36×10^{-4}	1.13	1.81×10^{-2}	0.72	0.0%

SNPs located in novel BCC susceptibility loci that met significance level after multiple testing corrections ($P < 1.69 \times 10^{-5}$) in the overall meta-analysis and also exhibited significant associations ($P < 0.05$) in both GWAS datasets with the same effect direction are listed. We used minor alleles as effect alleles in the analysis. Additionally, we report genetic locus, related DNA repair genes, major allele, minor allele, minor allele frequency (MAF) as calculated from overall meta-analysis, and odds ratio (OR) with P -value for each GWAS, calculated with respect to the minor allele. In 23andMe GWAS, we analyzed 12,945 self-reported BCC cases and 274,252 controls of European ancestry in the US. In Harvard GWAS, we analyzed 4,242 self-reported BCC cases and 12,802 controls of European ancestry in the US. We then combined the data from these 2 GWAS studies (which resulted in 17,187 cases and 287,054 controls) and performed fixed-effect meta-analysis. Statistics for effect heterogeneity were shown by P_{het} and I^2 .