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Research Article

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Germline Variants in DNA Repair Genes, Diagnostic Radiation, and Risk of Thyroid Cancer

Jason E. Sandler[1], Huang Huang[2], Nan Zhao[3], Weiwei Wu[3,4], Fangfang Liu[5,2], Shuangge Ma[6], Robert Udelsman[7], and Yawei Zhang[2,3]

Abstract

Background: Radiation exposure is a well-documented risk factor for thyroid cancer; diagnostic imaging represents an increasing source of exposure. Germline variations in DNA repair genes could increase risk of developing thyroid cancer following diagnostic radiation exposure. No studies have directly tested for interaction between germline mutations and radiation exposure.

Methods: Using data and DNA samples from a Connecticut population–based case–control study performed in 2010 to 2011, we genotyped 440 cases of incident thyroid cancer and 465 population-based controls for 296 SNPs in 52 DNA repair genes. We used multivariate unconditional logistic regression models to estimate associations between each SNP and thyroid cancer risk, as well as to directly estimate the genotype–environment interaction between each SNP and ionizing radiation.

Results: Three SNPs were associated with increased risk of thyroid cancer and with thyroid microcarcinoma: *HUS* rs2708896, *HUS* rs10951937, and *MGMT* rs12769288. No SNPs were associated with increased risk of larger tumor (>10 mm) in the additive model. The gene–environment interaction analysis yielded 24 SNPs with $P_{interaction} < 0.05$ for all thyroid cancer, 12 SNPs with $P_{interaction} < 0.05$ for thyroid microcarcinoma, and 5 SNPs with $P_{interaction} < 0.05$ for larger tumors.

Conclusions: Germline variants in DNA repair genes are associated with thyroid cancer risk and are differentially associated with thyroid microcarcinoma and large tumor size. Our study provides the first evidence that germline genetic variations modify the association between diagnostic radiation and thyroid cancer risk.

Impact: Thyroid microcarcinoma may represent a distinct subset of thyroid cancer. The effect of diagnostic radiation on thyroid cancer risk varies by germline polymorphism. *Cancer Epidemiol Biomarkers Prev; 27(3); 285–94. ©2017 AACR.*

Introduction

The link between ionizing radiation and thyroid cancer, particularly papillary thyroid carcinoma (PTC), has been well characterized in the literature. Given the rapidly increasing use of diagnostic radiation in health care settings, iatrogenic PTC is a potential sequela of routine medical workups (1) that should be mitigated as much as possible through primary prevention efforts.

DNA repair pathways work to protect the body from DNA damage caused by ionizing radiation and other mutagenic sources in the environment. These pathways include nonhomologous end joining, homologous recombination, nucleotide excision repair, and base excision repair, as well as direct reversal of DNA damage. Mutations in any of these pathways, whether acquired during life or inherited at birth, might alter an individual's lifetime risk of carcinogenesis, especially for individuals who have been exposed to higher lifetime doses of ionizing radiation.

The literature of recent years has started to examine the role of somatic mutations in PTC carcinogenesis, such as *RET*/PTC and other chromosomal arrangements (2, 3). However, the role of germline mutations in PTC development remains poorly documented. Furthermore, no studies to date have examined the role that such germline mutations might have in modifying the risk of PTC due to ionizing radiation. Here, we test the hypothesis that germline variations in DNA repair genes are associated with risk of PTC and, furthermore, that these variations further modify the effects of ionizing radiation on PTC risk. We do so by evaluating 299 SNPs in 52 genes related to DNA repair, using data from the Connecticut population–based case–control study.

Materials and Methods

Study participants

Details of the population-based case–control study were described in previous publications (1, 4). We identified cases of histologically confirmed, incident thyroid cancer via the Yale Cancer Center's Rapid Case Ascertainment Shared Resource. A total of 462 of the eligible cases (65.9% of all eligible cases) completed in-person interviews and were included in our study. Connecticut residents who had no lifetime history of cancer of any type were recruited via random-digit dialing as population-based

[1]Yale School of Medicine, New Haven, Connecticut. [2]Department of Surgery, Yale School of Medicine, New Haven, Connecticut. [3]Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut. [4]School of Public Health, Shanxi Medical University, Taiyuan, China. [5]The 302 Military Hospital, Beijing, China. [6]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut. [7]Endocrine Neoplasia Institute, Miami Cancer Center, Miami, Florida.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Yawei Zhang, Department of Surgery, Yale School of Medicine, Yale Cancer Center, 60 College Street LEPH 440, New Haven, CT 06520. Phone: 203-785-6210; Fax: 203-737-6023; E-mail: yawei.zhang@yale.edu

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controls. A total of 498 individuals participated as controls in the study. Cases and controls were frequency matched by age (±5 years). The study was approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. Written informed consent was obtained from each participant.

SNP genotyping

After undergoing the standardized interview process described previously, a total of 448 thyroid cancer cases and 465 controls donated samples of venipuncture whole blood. Peripheral blood leukocyte DNA was extracted using the Qiagen Phenol-Chloroform Extraction Kit (Qiagen, N.V.) according to standard manufacturer protocol. DNA was then genotyped using a custom-made Golden Gate Illumina assay. Genotyping data were successfully obtained for 440 thyroid carcinoma cases and 465 controls. The GoldenGate assay included analysis of 299 SNPs in 52 gene regions involved in DNA repair, based on statistical significance previously demonstrated at the SNP and gene levels in the 2011 analysis by Neta and colleagues (included in our analysis were all individual SNPs that had demonstrated a significance of $P_{snp} < 0.1$ in the study by Neta and colleagues, as well as all additional SNPs associated with gene regions with $P_{gene} < 0.1$ in the same study; ref. 5). Quality control duplicate samples were also included in the genotyping platform. All duplicate samples yielded a concordance rate of ≥99%. Hardy–Weinberg equilibrium (HWE) was assessed in controls for each SNP using a χ^2 test. SNPs with a $P > 0.00001$ from the χ^2 test were considered to be in HWE. Of the 299 SNPs tested, 3 SNPs were not in HWE and were excluded from the final analyses.

Statistical analysis

Unconditional logistic regression models were employed to estimate risk and to calculate ORs and 95% confidence intervals (CIs), adjusting for age, gender, and race. For each SNP of interest, the common homozygote was treated as the reference. We tested for linear trend using an additive model that assigned a value of 0 to common heterozygotes, 1 to heterozygotes (single variant), and 2 to rare homozygotes (double variant). We also compared the sum of heterozygotes and rare homozygotes with the common allele homozygote for each SNP to test for the collective significance of variation compared with the common allele. To control for race, subgroup analysis was performed using only Caucasian participants as the cases and controls. Further subgroup analysis was performed for PTC, PTC microcarcinoma ($n = 163$), and PTC large tumor size ($n = 168$). A final subgroup analysis used "PTC microcarcinoma" as cases and "PTC large tumor size" as controls.

Gene–environment interaction analysis

For the gene–environment interaction analysis, exposure to diagnostic radiation was defined as exposure to any of the following procedures: (i) upper gastrointestinal series; (ii) lower gastrointestinal series; (iii) chest X-rays; (iv) head and neck CT scans; (v) chest CT scans; (vi) abdominal CT scans; (vii) pelvic CT scans; (viii) nuclear cardiology tests; (ix) thyroid uptake studies using I-131 or another radioactive agent; (x) nuclear medicine tests, including bone, brain, liver scans, or other studies that utilize pretest injection of a radioactive agent; (xi) kidney X-rays involving dye injection into a vein or artery; and (xii) mammograms. Nonexposure was defined as lack of exposure to any of these 12 procedures. An unconditional logistic regression model was used to estimate the ORs and 95% CIs for association between exposure to diagnostic X-rays and risk of thyroid cancer and its subtypes in different genotypic strata. To increase statistical power, the heterozygous and homozygous variant genotypes were combined for each SNP and compared with the "common homozygous" genotype. The significance of gene–exposure interaction was assessed by adding an interaction term in the logistic models. Results were adjusted for age (continuous), gender, race, and body mass index (BMI).

We used an *a priori* significance level of 0.01 for each test rather than a Bonferroni correction because the Bonferroni correction is overly conservative when hypothesis tests are correlated (6, 7). A significance level of 0.01 will increase the type I error rate to the point of certainly identifying some false positive findings. However, it will also reduce the number of false negative findings and, thus, the actual α is likely to be substantially less than the nominal α in this case. All *P* values presented were two-sided. All analyses were performed using Statistical Analysis Software, version 9.3 (SAS Institute, Cary, NC).

Results

Table 1 displays selected demographic characteristics of cases and controls. Distribution of these characteristics was similar to that obtained for the original population (1). Supplementary Table S1 lists the genes represented in our analysis, grouped by category and displaying the number of analyzed SNPs per gene.

The results of the additive model SNP analysis were similar for thyroid cancer and for PTC. *HUS1* rs2708896 genotypes ($P_{trend} = 0.0057$), *HUS1* rs10951937 genotypes ($P_{trend} = 0.0070$), and *MGMT* rs12769288 genotypes ($P_{trend} = 0.0023$) were associated

Table 1. Distribution of selected characteristics among thyroid cancer cases and controls

	Cases ($n = 440$) Number (%)	Controls ($n = 465$) Number (%)	*P*
Age (years)			0.0001
<40	84 (19.1)	61 (13.1)	
40–49	112 (25.5)	117 (25.2)	
50–59	140 (31.8)	126 (27.1)	
60–69	78 (17.7)	94 (20.2)	
≥70	26 (5.9)	67 (14.4)	
Gender			<0.0001
Male	84 (19.1)	145 (31.2)	
Female	356 (80.9)	320 (68.8)	
Race			0.21
White	396 (90.0)	427 (91.8)	
Black	16 (3.6)	20 (4.3)	
Other	28 (6.4)	18 (3.9)	
BMI (kg/m^2)			0.0005
<25	140 (31.8)	185 (39.8)	
25–29.9	138 (31.4)	160 (34.3)	
≥30	159 (36.1)	112 (24.1)	
Missing	3 (0.7)	8 (1.7)	
Family history of thyroid cancer			0.0051
Yes	71 (16.1)	46 (9.9)	
No	369 (83.9)	419 (90.1)	
Benign thyroid disease			<0.0001
Yes	56 (12.7)	12 (2.6)	
No	384 (87.3)	453 (97.4)	

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Table 2. Statistically significant association between genotypes and risk of PTC among whites ($n = 760$)

Chromosome	Gene name	SNP	Genotype	Cases	Controls	OR (95% CI)	*P*
7	*HUS1*	rs2708896	GG	99	108	1	
			TG	171	199	0.92 (0.65–1.30)	0.641180875
			TT	63	120	0.55 (0.36–0.83)	0.004611807
			P_{trend}				0.00570544
			TG & TT	234	319	0.78 (0.56–1.08)	0.133937371
7	*HUS1*	rs10951937	TT	126	142	1	
			TG	161	185	0.98 (0.70–1.35)	0.886392195
			GG	46	100	0.51 (0.33–0.79)	0.002373343
			P_{trend}				0.00704081
			GG & TG	207	285	0.81 (0.60–1.10)	0.182937296
10	*MGMT*	rs12769288	CC	276	317	1	
			TC	55	101	0.62 (0.43–0.90)	0.012889857
			TT	2	9	0.23 (0.05–1.10)	0.065342142
			P_{trend}				0.0023066
			TC & TT	57	110	0.59 (0.41–0.85)	0.004426897

with PTC risk (Table 2). A number of other SNPs yielded statistically significant ORs for the heterozygous or the homozygous rare genotypes, but did not meet statistical significance in the additive model. These SNPs include *EME2* rs2076431, *MGMT* rs10764901, *RAD54B* rs2046666, *MBD4* rs4273365, and *ATR* rs10804682.

In the PTC subtype analysis, the variations in *HUS1* rs2708896, *HUS1* rs10951937, and *MGMT* rs12769288 all demonstrated statistically significant associations with PTC microcarcinoma in the additive model (Table 3). *MGMT* rs10764901, *MBD4* rs4273365, and *ATR* rs10804682, along with *RECQL* rs12312710, yielded statistically significant ORs for the heterozygous or the homozygous rare genotypes, but did not meet statistical significance in the additive model. No SNPs displayed statistically significant associations with PTC large tumor size in the additive model. However, a number of SNPs did yield statistically significant ORs for the less common genotypes. These SNPs include *EME2* rs2076431, *OGG1* rs159154, *OGG1* rs159153, *XAB2* rs1674034, *XAB2* rs794078, and *ATR* rs10804682. None of the SNPs listed above met statistical significance in the case–control analysis of microcarcinoma versus large tumor size.

We performed a *post hoc* analysis of the results for PTC large tumor size stratified by tumor size (11–15 mm, 16–30 mm, and >30 mm). This analysis revealed one SNP, rs1674034 in *XAB2*, that was significantly associated with PTC 16 to 30 mm ($P_{trend} = 0.0009$ for all races, $P_{trend} = 0.0059$ for Caucasians). No other SNPs remained significantly associated with any of the subgroups of PTC large tumor size after adjusting for race.

Supplementary Table S2 displays associations between diagnostic radiation exposure and risk of thyroid cancer among genotyped cases and controls. The results were similar to those obtained in the original 2015 analysis (1). The initial GxE analysis of thyroid cancer (Table 4) yielded 23 total SNPs with $P_{interaction} < 0.05$. Only 3 of these SNPs reached *a priori* significance of $P_{interaction} < 0.01$: *ALKBH3* rs10768994 ($P_{interaction} = 0.0086$), *LIG1* rs2163619 ($P_{interaction} = 0.0060$), and *LIG1* rs10421339 ($P_{interaction} = 0.0081$). Three more SNPs only achieved $P < 0.05$ but yielded large ORs: *MGMT* rs4750763 (OR = 3.79; CI, 1.44–9.98; $P_{interaction} = 0.015$), *MGMT* rs1762444 (OR = 3.36; CI, 1.37–8.27; $P_{interaction} = 0.024$), and *RPA3* rs4720751 (OR = 2.91; CI, 1.39–6.09; $P_{interaction} = 0.034$). When cases were restricted to PTC (Table 5), only *LIG1* rs2163619 and *LIG1* rs10421339 reached $P_{interaction} < 0.01$. In total, the SNPs with $P_{interaction} < 0.05$ for thyroid cancer included mutations in *ALKBH3* (7), *LIG1* (7), *TOPBP1* (3), *RPA3* (2), *MGMT* (2), *PARP4* (1), and *UBE2A* (1). The thyroid microcarcinoma subanalysis (Table 6) yielded 12 SNPs with $P_{interaction} < 0.05$, but only 1 SNP that reached *a priori* significance, *XRCC2* rs10234749 (OR = 7.82; CI, 2.20–27.78; $P_{interaction} = 0.0041$). Of the other 11 SNPs with $P_{interaction} < 0.05$, 4 were associated with *ALKBH3*, 4 were associated with *ERCC5*, and one was associated with *PARP4*. The subanalysis of PTC microcarcinoma (Supplementary Table S3)

Table 3. Statistically significant association between genotypes and risk of papillary thyroid microcarcinoma among whites ($n = 590$)

Chromosome	Gene name	SNP	Genotype	Cases	Controls	OR (95% CI)	*P*
7	*HUS1*	rs2708896	GG	53	108	1	
			TG	81	199	0.78 (0.51–1.21)	0.269937173
			TT	29	120	0.46 (0.27–0.79)	0.004725606
			P_{trend}				0.005150922
			TG & TT	110	319	0.66 (0.44–0.99)	0.047220849
7	*HUS1*	rs10951937	TT	68	142	1	
			TG	78	185	0.86 (0.57–1.28)	0.447883484
			GG	17	100	0.35 (0.19–0.65)	0.000708759
			P_{trend}				0.001602607
			GG & TG	95	285	0.68 (0.47–1.00)	0.048742011
10	*MGMT*	rs12769288	CC	141	317	1	
			TC	20	101	0.43 (0.25–0.73)	0.001710087
			TT	2	9	0.47 (0.10–2.26)	0.347352446
			P_{trend}				0.002130931
			TC & TT	22	110	0.43 (0.26–0.72)	0.001229464

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Table 4. Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of thyroid cancer ($n = 905$)

			Nonexposed			Exposed		
Chromosome	**Gene name**	**Genotype**	**Cases**	**Controls**	**OR[a] (95% CI)**	**Cases**	**Controls**	**OR[a] (95% CI)**
3	*TOPBP1_06*	rs17301766						
		CC	21	40	1.00	269	260	1.96 (1.06–3.66)
		TC or TT	15	12	1.00	134	152	0.81 (0.33–1.98)
		$P_{interaction}$						0.028
3	*TOPBP1_09*	rs11706586						
		CC	20	40	1.00	267	262	2.06 (1.10–3.86)
		TC or TT	15	12	1.00	135	151	0.85 (0.35–2.08)
		$P_{interaction}$						0.025
3	*TOPBP1_10*	rs7349558						
		AA	22	40	1.00	270	257	1.94 (1.05–3.59)
		AC or CC	14	12	1.00	133	156	0.79 (0.32–1.95)
		$P_{interaction}$						0.039
7	*RPA3_01*	rs4720751						
		TT	20	24	1.00	175	217	0.85 (0.43–1.71)
		TC or CC	15	28	1.00	227	196	2.91 (1.39–6.09)
		$P_{interaction}$						0.034
7	*RPA3_02*	rs17136898						
		AA	22	41	1.00	301	292	2.11 (1.15–3.88)
		AG or GG	13	11	1.00	101	121	0.78 (0.29–2.07)
		$P_{interaction}$						0.050
7	*XRCC2_01*	rs10234749						
		CC	19	36	1.00	279	251	2.51 (1.32–4.75)
		AC or AA	16	16	1.00	122	162	0.59 (0.25–1.44)
		$P_{interaction}$						0.025
10	*MGMT_02*	rs1762444						
		GG	8	25	1.00	158	161	3.36 (1.37–8.27)
		AG or AA	27	27	1.00	244	252	0.98 (0.52–1.85)
		$P_{interaction}$						0.024
10	*MGMT_32*	rs12219606						
		CC	8	21	1.00	139	143	2.55 (0.98–6.65)
		AC or AA	27	31	1.00	265	270	1.19 (0.65–2.16)
		$P_{interaction}$						0.049
10	*MGMT_36*	rs4750763						
		AA	7	26	1.00	165	171	3.79 (1.44–9.98)
		AC or CC	28	26	1.00	237	242	0.99 (0.54–1.85)
		$P_{interaction}$						0.015
11	*ALKBH3_03*	rs11037690						
		GG	14	32	1.00	203	193	2.43 (1.15–5.14)
		AG or AA	21	20	1.00	198	220	0.99 (0.48–2.02)
		$P_{interaction}$						0.029
11	*ALKBH3_14*	rs10768994						
		TT	8	26	1.00	137	131	2.88 (1.13–7.29)
		TC or CC	28	26	1.00	267	282	0.99 (0.53–1.84)
		$P_{interaction}$						0.0086
11	*ALKBH3_15*	rs10768995						
		GG	21	19	1.00	146	158	0.97 (0.45–2.09)
		GC or CC	14	33	1.00	256	255	2.37 (1.16–4.86)
		$P_{interaction}$						0.012
11	*ALKBH3_19*	rs868784						
		CC	11	29	1.00	169	155	2.66 (1.16–6.12)
		TC or TT	24	23	1.00	233	258	1.06 (0.54–2.05)
		$P_{interaction}$						0.018
11	*ALKBH3_20*	rs3893853						
		CC	20	38	1.00	275	247	2.01 (1.06–3.82)
		TC or TT	16	14	1.00	128	166	0.85 (0.36–1.98)
		$P_{interaction}$						0.014
11	*ALKBH3_21*	rs4755217						
		TT	8	26	1.00	137	133	2.86 (1.13–7.24)
		TC or CC	27	25	1.00	259	275	1.03 (0.55–1.95)
		$P_{interaction}$						0.014
11	*ALKBH3_22*	rs1973717						
		CC	20	20	1.00	155	165	1.10 (0.52–2.34)
		TC or TT	15	32	1.00	245	247	2.09 (1.03–4.26)
		$P_{interaction}$						0.045

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Table 4. Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of thyroid cancer ($n = 905$) (Cont'd)

			Nonexposed			Exposed		
Chromosome	Gene name	Genotype	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
13	*PARP4_04*	rs4770687						
		GG	14	13	1.00	99	121	0.62 (0.23–1.65)
		AG or AA	22	39	1.00	303	291	2.28 (1.24–4.19)
		$P_{interaction}$						0.043
19	*LIG1_01*	rs251693						
		TT	16	18	1.00	112	138	0.71 (0.32–1.61)
		TC or CC	19	34	1.00	291	275	2.51 (1.30–4.83)
		$P_{interaction}$						0.024
19	*LIG1_02*	rs2288878						
		GG	16	18	1.00	108	137	0.72 (0.32–1.61)
		AG or AA	20	34	1.00	294	276	2.36 (1.23–4.50)
		$P_{interaction}$						0.024
19	*LIG1_03*	rs274897						
		CC	16	18	1.00	109	138	0.69 (0.30–1.55)
		GC or GG	19	34	1.00	293	274	2.55 (1.32–4.91)
		$P_{interaction}$						0.020
19	*LIG1_04*	rs2386523						
		CC	14	15	1.00	86	103	0.73 (0.30–1.80)
		TC or TT	21	37	1.00	317	309	2.34 (1.25–4.38)
		$P_{interaction}$						0.025
19	*LIG1_05*	rs2163619						
		GG	13	13	1.00	73	95	0.57 (0.22–1.50)
		AG or AA	22	39	1.00	330	316	2.40 (1.30–4.42)
		$P_{interaction}$						0.0060
19	*LIG1_07*	rs274873						
		AA	14	16	1.00	95	111	0.59 (0.24–1.46)
		AG or GG	22	36	1.00	308	302	2.24 (1.21–4.15)
		$P_{interaction}$						0.035
19	*LIG1_10*	rs10421339						
		GG	15	15	1.00	94	113	0.45 (0.18–1.16)
		GC or CC	20	37	1.00	308	300	2.50 (1.34–4.69)
		$P_{interaction}$						0.0081
X	*UBE2A_01*	rs5910616						
		GG	33	43	1.00	309	328	1.28 (0.75–2.19)
		AG or GG	2	9	1.00	91	85	6.82 (1.08–43.08)
		$P_{interaction}$						0.043

[a]Adjusted for age (continuous), gender, race, and BMI.

yielded similar results. The subanalysis of thyroid cancer with large tumor size yielded 5 SNPs with $P_{interaction} < 0.05$ (Supplementary Table S4). Three of these SNPs reached *a priori* significance: *LIG1* rs251693 (OR = 2.20; CI, 1.02–4.73; $P_{interaction} = 0.0056$), *LIG1* rs2288878 (OR = 2.19; CI, 1.02–4.70; $P_{interaction} = 0.0040$), and *LIG1* rs274897 (OR = 2.26; CI, 1.05–4.87; $P_{interaction} = 0.0038$). When cases were restricted to PTC, none of the SNPs remained significant.

Discussion

The role of germline mutations in thyroid cancer and PTC has thus far received limited investigation. Gudmundsson and colleagues (8) performed a genome-wide association study (GWAS) to search for PTC susceptibility loci and uncovered two candidate SNPs. Individuals homozygous for both variant SNPs carried an estimated thyroid cancer risk more than five times greater than that of noncarriers. The authors replicated these results in two populations of European descent. Further studies have identified additional susceptibility loci (9, 10)

Most extant candidate gene studies of PTC have only examined up to 5 to 10 SNPs each (11–15). However, the study performed by Neta and colleagues in 2011 tested 5,077 SNPs from 340 candidate genes involved in genomic integrity (5). This study revealed 9 genomic integrity SNPs associated with PTC risk with $P_{trend} < 0.0005$, as well as 7 gene regions associated with PTC risk with $P_{trend} < 0.01$, although none of these SNPs remained statistically significant after adjustment for FDR. Three of the identified SNPs (*HUS1* rs2708906, *ALKBH3* rs10838192, and *MGMT* rs4751109), and two of the identified gene regions (*HUS1* and *ALKBH3*), correspond to genes involved in DNA repair. These promising results have merited validation.

Our study identifies a number of SNPs in DNA repair genes statistically significant associated with PTC. Among these genes are the three identified by Neta and colleagues: *HUS1*, *MGMT*, and *ALKBH3*. The HUS1 protein forms a complex with two other proteins, RAD1 and RAD9, and deposits in regions of damaged DNA. This activates the ATR kinase signaling cascade and thus the overall cellular response to DNA damage (16). MGMT repairs mutagenic methylguanine lesions generated by alkylating agents; decreased expression has been linked to increased incidence of gliomas (17) and testicular germ cell tumors (18). ALKBH3 plays a similar role by removing 1-methyladenine and 3-methylcytosine lesions from DNA (19).

Interestingly, our subanalysis reveals SNPs being differentially associated with PTC microcarcinoma and PTC larger tumor. For example, significant mutations in *HUS1* and *MGMT* were identified in microcarcinoma but not in larger tumor. Other mutations, such as those in *XAB2* and *OGG1*, only

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Table 5. Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of PTC ($n = 838$)

			Nonexposed			Exposed		
Chromosome	**Gene name**	**Genotype**	**Cases**	**Controls**	**OR[a] (95% CI)**	**Cases**	**Controls**	**OR[a] (95% CI)**
3	*TOPBP1_06*	rs17301766						
		CC	21	40	1.00	221	260	1.62 (0.86–3.06)
		TC or TT	14	12	1.00	116	152	0.79 (0.32–1.96)
		$P_{interaction}$						0.044
3	*TOPBP1_09*	rs11706586						
		CC	20	40	1.00	221	262	1.73 (0.91–3.27)
		TC or TT	14	12	1.00	115	151	0.81 (0.33–2.01)
		$P_{interaction}$						0.035
7	*RPA3_01*	rs4720751						
		TT	19	24	1.00	141	217	0.69 (0.33–1.41)
		TC or CC	15	28	1.00	196	196	2.73 (1.29–5.75)
		$P_{interaction}$						0.024
7	*HUS1_03*	rs3176595						
		GG	31	36	1.00	261	328	1.03 (0.59–1.82)
		AG or AA	4	16	1.00	74	84	4.20 (1.09–16.23)
		$P_{interaction}$						0.033
7	*XRCC2_01*	rs10234749						
		CC	18	36	1.00	231	251	2.24 (1.16–4.32)
		AC or AA	16	16	1.00	104	162	0.50 (0.20–1.24)
		$P_{interaction}$						0.026
10	*MGMT_02*	rs1762444						
		GG	8	25	1.00	131	161	2.86 (1.15–7.11)
		AG or AA	26	27	1.00	205	252	0.84 (0.44–1.62)
		$P_{interaction}$						0.025
10	*MGMT_36*	rs4750763						
		AA	7	26	1.00	137	171	3.49 (1.30–9.39)
		AC or CC	27	26	1.00	199	242	0.85 (0.45–1.59)
		$P_{interaction}$						0.016
11	*ALKBH3_03*	rs11037690						
		GG	13	32	1.00	171	193	2.16 (0.99–4.72)
		AG or AA	21	20	1.00	164	220	0.88 (0.43–1.81)
		$P_{interaction}$						0.026
11	*ALKBH3_14*	rs10768994						
		TT	8	26	1.00	115	131	2.40 (0.93–6.17)
		TC or CC	27	26	1.00	223	282	0.87 (0.46–1.63)
		$P_{interaction}$						0.010
11	*ALKBH3_15*	rs10768995						
		GG	21	19	1.00	124	158	0.83 (0.38–1.80)
		GC or CC	13	33	1.00	212	255	2.21 (1.05–4.64)
		$P_{interaction}$						0.011
11	*ALKBH3_19*	rs868784						
		CC	10	29	1.00	144	155	2.40 (1.01–5.72)
		TC or TT	24	23	1.00	193	258	0.92 (0.47–1.80)
		$P_{interaction}$						0.014
11	*ALKBH3_20*	rs3893853						
		CC	19	38	1.00	231	247	1.72 (0.89–3.34)
		TC or TT	16	14	1.00	106	166	0.74 (0.31–1.74)
		$P_{interaction}$						0.013
11	*ALKBH3_21*	rs4755217						
		TT	8	26	1.00	116	133	2.47 (0.96–6.32)
		TC or CC	26	25	1.00	214	275	0.90 (0.47–1.72)
		$P_{interaction}$						0.015
11	*ALKBH3_22*	rs1973717						
		CC	20	20	1.00	133	165	0.95 (0.44–2.04)
		TC or TT	14	32	1.00	201	247	1.89 (0.91–3.96)
		$P_{interaction}$						0.048
13	*PARP4_04*	rs4770687						
		GG	13	13	1.00	80	121	0.56 (0.20–1.55)
		AG or AA	22	39	1.00	256	291	1.92 (1.04–3.54)
		$P_{interaction}$						0.042
19	*LIG1_01*	rs251693						
		TT	16	18	1.00	93	138	0.55 (0.24–1.28)
		TC or CC	18	34	1.00	244	275	2.33 (1.19–4.56)
		$P_{interaction}$						0.019

(Continued on the following page)

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Table 5. Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of PTC ($n = 838$) (Cont'd)

			Nonexposed			Exposed		
Chromosome	Gene name	Genotype	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
19	*LIG1_02*	rs2288878						
		GG	16	18	1.00	90	137	0.55 (0.24–1.28)
		AG or AA	19	34	1.00	246	276	2.20 (1.13–4.27)
		$P_{interaction}$						0.020
19	*LIG1_03*	rs274897						
		CC	16	18	1.00	90	138	0.52 (0.22–1.21)
		GC or GG	18	34	1.00	246	274	2.38 (1.22–4.67)
		$P_{interaction}$						0.015
19	*LIG1_04*	rs2386523						
		CC	14	15	1.00	72	103	0.56 (0.22–1.43)
		TC or TT	20	37	1.00	265	309	2.16 (1.14–4.10)
		$P_{interaction}$						0.020
19	*LIG1_05*	rs2163619						
		GG	13	13	1.00	61	95	0.39 (0.14–1.12)
		AG or AA	21	39	1.00	276	316	2.19 (1.17–4.09)
		$P_{interaction}$						0.0044
19	*LIG1_07*	rs274873						
		AA	14	16	1.00	79	111	0.43 (0.16–1.11)
		AG or GG	21	36	1.00	258	302	2.07 (1.10–3.90)
		$P_{interaction}$						0.026
19	*LIG1_10*	rs10421339						
		GG	15	15	1.00	79	113	0.34 (0.12–0.91)
		GC or CC	19	37	1.00	257	300	2.29 (1.20–4.36)
		$P_{interaction}$						0.0066
X	*UBE2A_01*	rs5910616						
		GG	32	43	1.00	256	328	1.11 (0.64–1.92)
		AG or AA	2	9	1.00	80	85	6.35 (1.00–40.40)
		$P_{interaction}$						0.034

[a]Adjusted for age (continuous), gender, race, and BMI.

showed association with larger tumor. None of these SNPs yielded significant values in the head-to-head comparison of microcarcinoma versus larger tumor (one possible explanation could be that some "microcarcinoma" cases in fact represent a misclassification of larger tumors in their early stages of development). The differential association of SNPs with tumor sizes suggests that there might be underlying biological differences between microcarcinomas and larger tumors, which would merit further genomic investigation.

Our study is the first to examine interaction between SNPs and lifetime exposure to ionizing radiation. The GxE analyses revealed significant SNPs linked to *MGMT* and *ALKBH3* (described previously) as well as in four additional genes: *ERCC5*, *PARP1*, *XRCC2*, and *LIG1*. The ERCC5 endonuclease makes the 3′ incision in DNA excision repair following UV-induced damage (20). Genetic variation in *ERCC5* has been associated with risk of lung cancer (21), gastric cancer (22), and xeroderma pigmentosum (23). XRCC2 and PARP1 are both involved in homologous recombination. XRCC2-deficient cells appear more sensitive to PARP1 inhibitors than XRCC2-expressing cells, suggesting that XRCC2 and PARP1 share a DNA repair pathway (24). The LIG1 ligase is involved in DNA replication, recombination, and base excision repair (25); *LIG1* germline polymorphisms have been associated with non–small cell lung cancer (26, 27). SNPs in *LIG1* appeared to be most strongly associated with larger tumor in this study, whereas the SNPs in *ERCC5*, *PARP1*, and *XRCC2* displayed association with microcarcinoma.

None of our significant SNPs were in protein-coding regions. SNPs within introns might affect RNA splicing patterns and thus upregulate or downregulate key DNA repair protein products (28). In particular, SNPs that alter the usual pattern of exonic splicing enhancers (ESE) could affect spliceosome assembly and lead to exon skipping (29). To investigate this hypothesis, we used ESEFinder (Cold Spring Harbor Laboratory) to test 43 of our most significant SNP "hits" for changes in their pattern of ESEs. Thirty-three SNPs demonstrated the potential to modify at least one ESE (Supplementary Table S5). SNPs located upstream of genes could be involved with promotor or regulator sequences, influencing the amount of RNA transcribed in various biological circumstances (30). Mounting evidence suggests that a majority of gene–environment interaction is determined by distant regulatory sequences (31). We did not directly test for cellular RNA or protein content, but further biological experiments could test for evidence differential gene transcription and RNA modification.

An important limitation of the current study is the sample size, which, although larger than those of previous candidate SNP studies, still proved insufficient to detect SNPs with unequivocal statistical significance after Bonferroni correction for multiple comparison. SNP validation would require an even larger pool of cases and controls. A larger sample size would also increase confidence in certain "significant" results that are based on very small sample sizes. Finally, although our *post hoc* analysis of large tumor size subsets suggests that additional SNP associations might exist, the current study was not powered to detect such associations.

Recall bias must be considered in this study. Data on diagnostic radiography exposure relied upon self-reporting by cases and controls, rather than health record documentation. However, as described in our previous publication, other studies (32–34) have suggested nondifferential reporting error between thyroid cancer cases and controls. Even if differential recall bias were a possibility for subjects in a particular age

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Table 6. Statistically significant effect modification of genotypes between diagnostic radiation exposure and risk of thyroid microcarcinoma ($n = 672$)

			Nonexposed			Exposed		
Chromosome	**Gene name**	**Genotype**	**Cases**	**Controls**	**OR[a] (95% CI)**	**Cases**	**Controls**	**OR[a] (95% CI)**
7	*XRCC2_01*	rs10234749						
		CC	3	36	1.00	135	251	7.82 (2.20–27.78)
		AC or AA	6	16	1.00	60	162	0.65 (0.20–2.11)
		$P_{interaction}$						0.0041
10	*MGMT_33*	rs10829618						
		GG	3	41	1.00	122	264	7.16 (2.02–25.39)
		GC or CC	6	11	1.00	75	149	0.99 (0.32–3.12)
		$P_{interaction}$						0.036
10	*MGMT_39*	rs4751112						
		AA	3	39	1.00	118	256	6.78 (1.89–24.30)
		AG or GG	7	13	1.00	79	157	1.01 (0.34–2.99)
		$P_{interaction}$						0.045
11	*ALKBH3_01*	rs12804822						
		AA	2	33	1.00	109	232	8.92 (1.96–40.55)
		AC or CC	7	19	1.00	88	181	1.23 (0.44–3.46)
		$P_{interaction}$						0.022
11	*ALKBH3_07*	rs3740983						
		TT	2	32	1.00	104	224	9.52 (2.07–43.81)
		TG or GG	7	20	1.00	93	189	1.29 (0.47–3.53)
		$P_{interaction}$						0.030
11	*ALKBH3_08*	rs7482199						
		TT	2	34	1.00	103	231	8.97 (1.97–40.92)
		TC or CC	8	18	1.00	94	182	1.15 (0.43–3.07)
		$P_{interaction}$						0.018
11	*ALKBH3_11*	rs11037726						
		AA	2	34	1.00	106	233	9.01 (1.97–41.15)
		TA or TT	8	18	1.00	91	179	1.17 (0.44–3.15)
		$P_{interaction}$						0.017
13	*PARP4_04*	rs4770687						
		GG	6	13	1.00	48	121	0.62 (0.18–2.16)
		AG or AA	4	39	1.00	148	291	5.73 (1.89–17.40)
		$P_{interaction}$						0.020
13	*ERCC5_07*	rs4150355						
		GG	7	22	1.00	77	173	1.35 (0.49–3.69)
		AG or AA	2	30	1.00	120	240	8.01 (1.72–37.23)
		$P_{interaction}$						0.033
13	*ERCC5_11*	rs17655						
		GG	9	29	1.00	102	244	0.95 (0.39–2.35)
		CG or CC	1	23	1.00	95	169	21.97 (2.74–176.47)
		$P_{interaction}$						0.030
13	*ERCC5_13*	rs9586002						
		GG	2	31	1.00	120	243	8.88 (1.96–40.16)
		TG or TT	7	21	1.00	77	170	1.11 (0.40–3.10)
		$P_{interaction}$						0.033
13	*ERCC5_14*	rs1886087						
		AA	6	16	1.00	52	111	1.47 (0.47–4.62)
		TA or TT	3	36	1.00	145	302	5.77 (1.62–20.54)
		$P_{interaction}$						0.036

[a]Adjusted for age (continuous), gender, race, and BMI.

range (35), our age-stratified analysis of the original data described previously was unable to uncover evidence of such bias in our own findings. Furthermore, our significant findings are limited to thyroid microcarcinoma. In addition, diverse types of diagnostic radiation exposure were combined, which might cause potential exposure misclassification. In gene–environment interaction studies, both differential and non-differential misclassification of a binary environmental factor biases a multiplicative interaction effect toward the null (36).

As previously discussed, our candidate gene approach likely misses many potentially significant regions of the genome. A fruitful future direction for this work would be performing a GWAS using a randomly selected subset of our cases and controls, to identify novel regions of genomic significance.

Conclusion

This study provides further evidence that germline mutations in DNA repair genes are significantly associated with risk of thyroid cancer and PTC. It suggests that microcarcinoma, which is particularly associated with diagnostic radiation exposure, represents a distinct subset of thyroid cancer and PTC with its own biological signature. Finally, our study provides novel evidence to suggest a significant interaction between germline mutations in DNA repair genes and ionizing radiation in the pathogenesis of thyroid cancer. These results merit replication with larger sample sizes and alternative study methods to establish statistical significance, and to further explore the basis of the molecular biology behind them.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these results.

Authors' Contributions

Conception and design: R. Udelsman, Y. Zhang
Development of methodology: J.E. Sandler, Y. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.E. Sandler, H. Huang, N. Zhao, W. Wu, F. Liu, S. Ma, R. Udelsman
Writing, review, and/or revision of the manuscript: J.E. Sandler, H. Huang, S. Ma, R. Udelsman, Y. Zhang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Zhao, F. Liu, Y. Zhang
Study supervision: Y. Zhang

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Jason E. Sandler, Huang Huang, Nan Zhao, et al.

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