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Common genetic variants in the 8q24 region and risk of papillary thyroid cancer

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Abstract

Objectives/Hypothesis—Single nucleotide polymorphisms (SNPs) in the 8q24 chromosomal region identified from genome-wide scans have been associated with risk of several cancers including breast (rs1562430), prostate and colon (rs1447295 and rs6983267). A genome-wide scan in 26 families with papillary thyroid cancer (PTC) also found susceptibility loci in 8q24, supporting a closer evaluation of this chromosomal region in relation to risk of sporadic PTC.

Study Design—We evaluated 157 tag SNPs in the 8q24 chromosomal region between 120.91 Mb and 128.78 Mb (including rs1562430, rs1447295, and rs6983267) in a case-control study of 344 PTC cases and 452 age and gender frequency-matched controls.

Methods—We used logistic regression to estimate odds ratios and compute *P*-values of linear trend for PTC with genotypes of interest. To account for multiple comparisons, we applied the false discovery rate (FDR) method.

Results—We did not find a significant association between rs1562430, rs1447295, or rs6983267, and PTC risk. We found that one SNP (rs4733616) was associated with PTC risk at *P* = 0.003, and twelve other SNPs were associated with PTC risk at *P* < 0.05. However, no SNPs remained significant after FDR correction.

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Conflict of Interest: None

Conclusions—Our findings do not support a strong association between SNPs in the 8q24 chromosomal region and risk of sporadic PTC but several SNPs with small effects might exist.

Keywords

8q24; thyroid cancer

Introduction

Single nucleotide polymorphisms (SNPs) in the 8q24 chromosomal gene-poor region, known as 'gene desert', have been consistently implicated in genome-wide association studies as susceptibility loci for several cancer sites including breast, prostate and colorectal cancers¹⁻⁶. Some of these SNPs (rs6983267) appear to confer susceptibility to multiple cancers^{7,8}, and others (rs1562430 and rs1447295) have been repeatedly identified in several genome-wide association studies^{2,7-9}. One case-control study of 485 sporadic thyroid cancer cases found a weak association between rs6983267 and thyroid cancer risk, but this result has not been reproduced and only the single marker in the 8q24 region was examined, leaving the possibility for other susceptibility loci in 8q24⁸. Interestingly, a genome-wide association study examining the risk of heritable papillary thyroid cancer (PTC) among 26 families identified additional susceptibility loci in the 8q24 region¹⁰. To evaluate whether the 8q24 region might contain genetic variants associated with risk of sporadic thyroid cancer, we genotyped 157 tag SNPs between 120.91 Mb and 128.78 Mb in a case-control study of 344 PTC cases and 452 controls, using a platform that was created to analyze genetic susceptibility to a variety of rare cancers.

Materials and Methods

Our subjects included 202 incident PTC cases diagnosed within the U.S. Radiologic Technologists (USRT) cohort¹¹, 142 incident PTC cases diagnosed and treated at the University of Texas M. D. Anderson Cancer Center (UTMDACC)¹², and 452 age and gender frequency-matched controls from the USRT study, matched to USRT cases (90.6% female). The proportion of females among the UTMDACC cases was lower (64.1%) than in the USRT cohort. All study subjects were of European ancestry. All PTC cases included in this study were histologically confirmed. To ensure that the cases from the two studies were comparable, we compared average age at diagnosis, smoking status and tumor size, and found that the two case series were similar (Supplemental Table 1). Both studies were reviewed and approved by their respective Institutional Review Boards and all subjects provided informed consent.

Genotyping of 157 tag SNPs in the 8q24 region located between 120.91 and 128.79 Mb was performed at the National Cancer Institute's Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD; <http://cgf.nci.nih.gov/>) using the custom-designed iSelect Infinium assay (Illumina, www.illumina.com). Tag SNPs were selected from the common SNPs (minor allele frequency, MAF > 5%) genotyped by the HapMap Project (Data Release 20/Phase II, NCBI Build 36.1, assembly dbSNPb126) in the Caucasian population (CEU) using TagZilla, which is a part of the GLU software package (<http://code.google.com/p/glu-genetics/>) with a binning threshold of $r^2 > 0.8$. Previously identified hits from genome-wide association studies of other common cancers, including breast (rs1562430), and prostate and colon (rs1447295 and rs6983267) were also included. In the analysis, SNPs were excluded if they failed quality control measures: <95% concordance, <90% completion, or had evidence of a departure from Hardy-Weinberg equilibrium in controls ($P < 0.00001$). Allele frequencies for PTC cases were largely similar

between the USRT and the UTMDACC cases and between males and females, so these groups were combined for genetic analyses.

We calculated the linear P_{trend} for each SNP genotype, coded as 0, 1, 2, with 0 denoting the homozygous common allele genotype as the referent category, in logistic regression models adjusted for sex, attained age at diagnosis in four categories (<35, 35-44, 45-54, 55+ years), and year of birth (<1940, 1940-1949, 1950+) as an ordinal variable. We also evaluated the effect of additional adjustment for cigarette smoking. The results from the models with additional adjustments were similar and we chose to present the results from basic models adjusted for sex, attained age and year of birth only. We corrected for multiple comparisons using the false discovery rate control (FDR) method¹³. Statistical analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC) and in *R*.

Results

Demographic characteristics of the 344 PTC cases and 452 controls have been reported previously¹⁴ and are presented in supplemental material here (Supplemental Table 2). The age distribution was similar between cases and controls. Cases were more likely to report increased BMI and a family history of any cancer or of thyroid cancer specifically; but less likely to report history of smoking.

In logistic regression analyses, polymorphisms at rs1562430, rs6983267, and rs1447295 were not associated with PTC risk ($P = 0.15$, $P = 0.64$, and $P = 0.23$, respectively) (Figure 1). One SNP (rs4733616) was associated with PTC risk at $P = 0.003$, and 12 additional SNPs at $P < 0.05$ (Table 1). None of these SNPs were in linkage disequilibrium with the previously identified loci in genome-wide association studies (Figure 1). After FDR correction, no SNPs were significantly associated with PTC risk. Raw and FDR corrected P -values for all 157 tag SNPs are presented in supplemental material (Table S3).

Discussion

Our study is the first to closely examine sporadic PTC risk in relation to densely selected SNPs in the 8q24 chromosomal region previously associated with risk of multiple cancers including breast cancer. The latter association is particularly intriguing given increased risk of breast cancer in women with a history of prior thyroid cancer reported by the Surveillance Epidemiology and End Results database studies¹⁵. Several observational studies have also reported an increased risk of thyroid cancer with a history of benign breast disease^{16,17}. While the association between thyroid and breast diseases in epidemiologic studies could in part be explained by greater medical surveillance of cancer survivors, it may also be due to common underlying genetic mechanisms.

We found that none of the SNPs in the 8q24 region previously associated with other cancers were significantly associated with risk of sporadic PTC in our study, but several other SNPs across the region were. While none of the significant associations persisted after correction for multiple comparisons, our FDR adjustment may be overly conservative because SNPs in the 8q24 region appear to have a higher prior probability of being associated with PTC risk. Nonetheless, our findings do not provide evidence for a strong association between SNPs in the 8q24 region and risk of thyroid cancer.

Moreover, we found that PTC risk was not associated with the SNP rs6983267 consistently linked with prostate cancer, for which results from a previous thyroid cancer study were suggestive⁸. The results of our study are consistent with a recent case-control study of 398 cases of differentiated thyroid cancer (339 PTC) that examined two SNPs in the 8q24 region (rs6983267 and rs1447295) and found no association¹⁸.

Given that PTC cases were less likely to be cigarette smokers, we explored whether cigarette smoking may have influenced the associations of interest. When added to the models, cigarette smoking did not meaningfully change the risk estimates, and therefore, is unlikely to confound our main findings.

A limitation of our study is that while we had extensive coverage for a particular region of 8q24, we did not scan the entire 8q24 region, leaving the possibility that other susceptibility loci beyond the genotyped area might have been missed. Moreover, we had limited statistical power to detect weak associations. However, by narrowing our scope to areas of 8q24 previously implicated in a variety of other common cancers in genome-wide scans, we tried to increase the prior probability and to minimize the multiple testing problems.

Conclusion

In summary, our study is the first study to examine a large number of SNPs in the 8q24 chromosomal region in relation to risk of sporadic PTC. We found little evidence for a strong association of 157 tag SNPs in the 8q24 chromosomal region with risk of PTC, but small effects might exist for several SNPs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Significance levels (P values) from logistic regression analyses of tag SNPs in the intergenic region of 8q24 and risk of papillary thyroid cancer.

For markers above the $P = 0.05$ line, see Table 1. For markers below the $P = 0.05$ line:

☒ rs6983267 previously associated with prostate and colorectal, and thyroid (not GWAS).

⊞ rs1447295 previously associated with prostate cancer.

▽ rs9642880 previously associated with bladder and urinary cancer.

▣ rs4242382 and rs4242384 previously associated with prostate cancer.

◆ rs1562430 previously associated with breast cancer ².

△ rs2456449 previously associated with chronic lymphocytic leukemia ¹⁹.

For more information on these SNPs in genome-wide association studies, see <http://hugenavigator.net/HuGENavigator/gWAHitStartPage.do>.

Table 1

SNPs in intergenic region of 8q24 with an uncorrected $P < 0.05$ for an association with papillary thyroid cancer.

SNP	Location	Gene	P value ^a	P_{FDR} value ^b
rs4733616	128731277		0.003	0.464
rs1562432	128576784		0.011	0.566
rs4871808	128582727		0.015	0.566
rs12543106	128642480		0.024	0.566
rs377649	128406423		0.027	0.566
rs2466035	128280411		0.029	0.566
rs10087719	128298045		0.030	0.566
rs424281	128408608		0.031	0.566
rs13249993	128419697		0.034	0.566
rs7816475	128294622		0.043	0.566
rs4733655	128638038		0.045	0.566
rs4385433	128734662		0.046	0.566
rs2124600	128241868	SRRM1L	0.047	0.566

^aSNP-based linear P_{trend} calculated based on the three-level genotype (0, 1, and 2) in logistic regression models adjusted for sex, attained age, and year of birth.

^bFalse discovery rate (FDR) corrected linear P_{trend} .