Association of rs6983267 Polymorphism and Thyroid Cancer Susceptibility: A Systematic Review and Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Recent genome-wide association studies have identified rs6983267 polymorphism as a key locus in the 8q24 region associated with multisite cancers. However, the information on its association with thyroid cancer is inconclusive. The aim of this study was to determine whether this locus is a risk factor for susceptibility to thyroid cancer by conducting a meta-analysis.

Material/Methods: Relevant studies were identified by searching PubMed and Embase databases. The pooled odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated.

Results: A total of 4 studies including 2825 cases and 9684 controls were enrolled to this meta-analysis. The pooled data showed the G allele of the rs6983267 polymorphism is a risk factor for susceptibility to thyroid cancer (OR=1.08, 95%CI: 1.02–1.16, P=0.01). Significant associations were also found in homozygote comparison (GG vs. TT: OR=1.17, 95%CI: 1.03–1.33, P=0.02) and dominant model (GG+GT vs. TT: OR=1.13, 95%CI: 1.01–1.26, P=0.03). Borderline significant associations in similar directions were found in the recessive model (GG vs. GT+TT: OR=1.10, 95%CI: 0.99–1.22, P=0.07) and heterozygote comparison (GT vs. TT: OR=1.10, 95%CI: 0.99–1.24, P=0.09).

Conclusions: Our meta-analysis shows that the rs6983267 G>T polymorphism might be associated with higher risk of thyroid cancer. Further research with larger sample sizes and full investigation of confounding risk factors is needed to confirm or revise our conclusions.

MeSH Keywords: **Genetic Predisposition to Disease • Meta-Analysis • Thyroid Neoplasms**

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Background

Thyroid cancer (TC) is the most common endocrine malignancy [1] and may be caused by environmental and genetic factors. Family history is known to be a strong risk factor for thyroid cancer. An approximately 3- to 4-fold or higher increased risk for TC was reported among patients who have a first-degree relative with TC [2,3]. It has been acknowledged that single-nucleotide polymorphisms (SNP) could account for part of the hereditary susceptibility to cancer [4].

Recent genome-wide association studies (GWASs) have identified rs6983267 in chromosome 8q24 as a new susceptibility locus for several cancers, including breast, prostate, and colorectal cancer [5–8]. Associations between the rs6983267 polymorphism and TC in different populations have been investigated [9–14], but the published results are inconsistent due to some potential limitations, such as small sample size, different ethnicity, phenotypic heterogeneity, and study design. Therefore, we performed a systematic review and meta-analysis of the published studies to clarify this inconsistency and provide a more comprehensive picture of the relationship between rs6983267 polymorphism and TC susceptibility.

Material and Methods

Literature search strategy

All genetic association studies on rs6983267 polymorphism and TC published before March 1, 2015 were sought by searching databases (PubMed, Embase, ISI Web of Knowledge, Science Direct, and Cochrane databases) using "thyroid carcinoma" or "thyroid cancer" as free-text words combined with "8q24", "rs6983267", "polymorphism" or "susceptibility". Related MeSH terms were used in the PubMed database. Two authors (Li JD and Wang XF) independently scanned the title and abstract of every retrieved record to exclude those that were obviously irrelevant. Full articles of the remaining trials were retrieved for further assessment to identify relevant articles. In addition, we also reviewed all references cited in the identified articles.

Inclusion and exclusion criteria

The inclusion criteria for eligible studies were: (1) cohort or case-control study; (2) evaluated the association of rs6983267 polymorphism and TC risk; (3) included at least 2 comparison groups (TC and control groups); and (4) provided sufficient data to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI). Overlapping studies, case-only studies, and review articles were excluded.

Data extraction and quality assessment

Two investigators (Li JD and Wang XF) independently extracted data from each original article, including first author name, publication year, ethnicity, source of controls, genotyping method, sample size (numbers of cases and controls), and genotype frequency. The Newcastle-Ottawa Scale (NOS) for cohort or case-control studies was used to assess the quality of included studies. Detailed information for quality assessment by NOS was previously described [15]. The full score was 9 stars, with ≥7 stars defined as a high-quality study. Discrepancies were discussed and resolved by consensus.

Statistical analysis

We investigated Hardy-Weinberg equilibrium in the control groups of individual studies by using the goodness-of-fit χ^2 statistic with 1 degree of freedom. A P value more than 0.05 was considered to be consistent with Hardy-Weinberg equilibrium.

To evaluate the strength of the association between rs6983267 polymorphism and TC risk, the summarized odds ratio (OR) and its 95% confidence interval (CI) were calculated under various genetic models: the dominant model (GG+GT vs. TT), the recessive model (GG vs. GT+TT), the homozygote comparison (GG vs. TT), the heterozygote comparison (GT vs. TT), and allele contrast (G vs. T) by fixed-effects model [16] or random-effects model [17] based on the heterogeneity. The heterogeneity among individual trials was assessed by the I^2 test and Q-test [18]. The P value of Q-test <0.1 indicated evidence of significant statistical heterogeneity. When heterogeneity was present, the random-effects model was used to pool the data; otherwise the fixed-effects model was used. Publication bias was examined using a funnel plot. All P values were 2-sided and the type I error was set at 0.05. All data analyses were performed using RevMan software version 5.02 (Cochrane Collaboration, Oxford, England). This article was performed according to the PRISMA statement for reporting systematic reviews [19].

Results

Study characteristics

The literature review identified 826 reports that met the search criteria. As shown in Figure 1, after further evaluation for eligibility, only 4 studies [10,13,20,21] fulfilled the inclusion criteria, including 2825 cases and 9684 controls. All studies were published in English and they were all case-control study designs. All were conducted in Europe. Table 1 presents the main characteristics of these studies. The genotype distribution in the controls was consistent with Hardy-Weinberg equilibrium
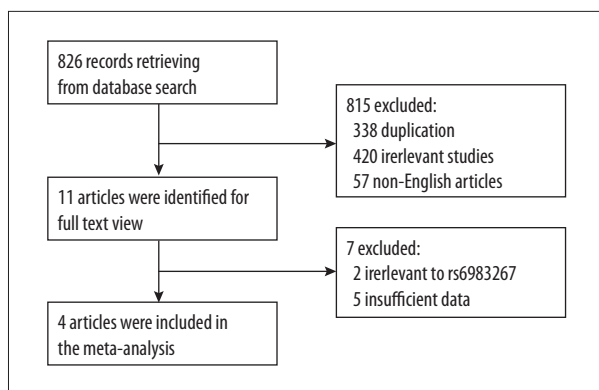
Figure 1. Flow chart of article selection.

in all studies. Three studies used the same method of genotyping for cases and controls, but the cases and controls were genotyped with a different method in another study [21]. All cases were histologically confirmed.

Meta-analysis results

As shown in Figure 2, the G variant of the rs6983267 polymorphism was associated with a higher risk of TC. The pooled analysis of 4 studies showed a significant increase in TC risk in the homozygote comparison (GG *vs.* TT: OR=1.17, 95%CI: 1.03–1.33, *P*=0.02), dominant model (GG+GT *vs.* TT: OR=1.13, 95%CI: 1.01–1.26, *P*=0.03), and allele contrast (G *vs.* T: OR=1.08, 95%CI: 1.02–1.16, *P*=0.01). Borderline-significant associations with similar directions were found in the recessive model (GG *vs.* GT+TT: OR=1.10, 95%CI: 0.99–1.22, *P*=0.07) and heterozygote comparison (GT *vs.* TT: OR=1.10, 95%CI: 0.99–1.24, *P*=0.09). The heterogeneity was negligible among all the studies in each analysis (*P*>0.1), except for the recessive model analysis (I^2=60%, *P*=0.06).

Sensitivity analyses and publication bias

Sensitivity analyses were performed by omitting each study one at a time to assess the effect of each individual study on the pooled OR. The results showed that the studies by Jones et al. [21] and Wokolorczyk et al. [13] significantly affected the

pooled ORs of homozygote comparison, dominant model, and allele contrast. The symmetrical shape of the funnel plot indicated no publication bias for all the results.

Discussion

The etiology of TC is poorly understood at present. Accumulating evidence suggests that the contribution of genetics to the risk of TC is greater than in most other cancers. The common variation of rs6983267 is associated with the risk of several cancers, including those of prostate, colon, and breast, and was assessed as a TC susceptibility gene for this reason. A significant association between rs6983267 SNP and TC was found in the Polish [13] and United Kingdom [21] populations, but no association was found in Spanish [20], Italian [10], or Japanese [22] populations, perhaps due to small sample sizes and/or alleles distribution differences among different populations. Therefore, it is important to quantitatively evaluate the effect of rs6983267 SNP in different populations and to investigate potential heterogeneity of published data. To the best of our knowledge, this is the first systematic review and meta-analysis that assessed the rs6983267 SNP and susceptibility to TC. The present study involved 4 studies including 2825 cases and 9684 controls. Our findings demonstrated that the rs6983267 polymorphism may be a risk factor for TC.

It should be noted that the results were unstable because confidence intervals of ORs for homozygote comparison, dominant model, and allele contrast throughout were very close to the non-significant range, and 2 studies significantly affected these pooled ORs in sensitivity analyses. In addition, significant heterogeneity among studies was also detected in the recessive model analysis (I^2=60%, *P*=0.06). Both of these can be explained by the different genetic and environmental backgrounds in different populations. The allele G at rs6983267 has a large effect on population prevalence of TC because of its high frequency, varying from 31% in native Hawaiians to 85% in African Americans [23]. Although the risk allele frequency of rs6983267 is approximately 50% (48~53%) in the 4 European populations, the allele distribution was significantly

Table 1. Main characteristics of the studies included in this meta-analysis.

Study	Year	Country	Sample size (case/control)	Genotype frequency (case/control)			Genotyping method	Quality score (★)
				GG	GT	TT		
Cipollini	2013	Italy	1200/1196	292/307	630/599	278/290	TaqMan	7
Wokolorczyk	2008	Poland	485/1910	122/420	254/977	109/513	PCR-RFLP	9
Akdi	2011	Spanish	389/463	114/142	187/204	88/117	iPLFX	9
Jones	2012	UK	751/6115	241/1662	346/3012	164/1441	KAspar; SNP array	8

PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism assay.

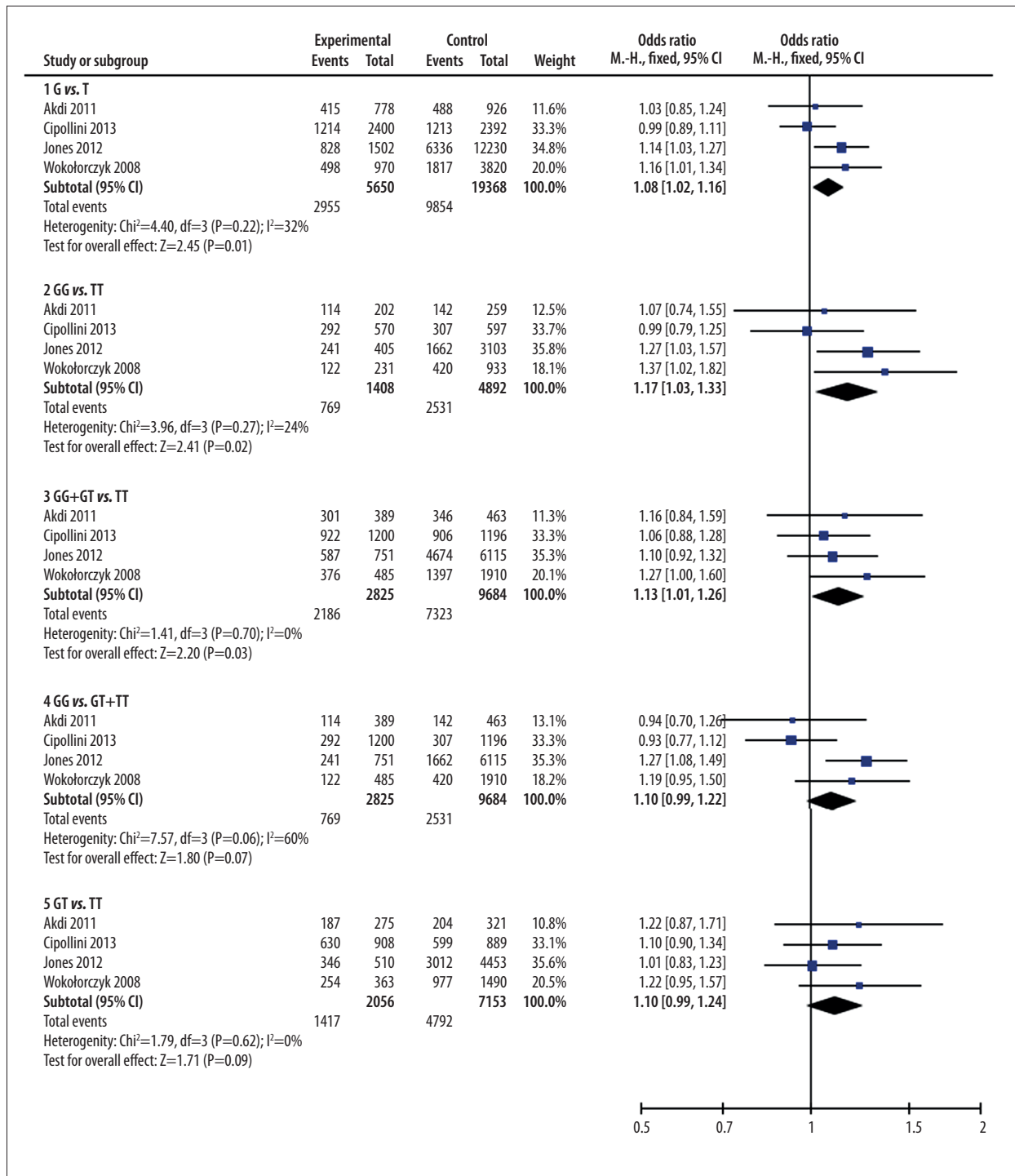| Study or subgroup	Experimental		Control		Weight	Odds ratio M.-H., fixed, 95% CI	Odds ratio M.-H., fixed, 95% CI
	Events	Total	Events	Total			
1 G *vs.* T							
Akdi 2011	415	778	488	926	11.6%	1.03 [0.85, 1.24]	
Cipollini 2013	1214	2400	1213	2392	33.3%	0.99 [0.89, 1.11]	
Jones 2012	828	1502	6336	12230	34.8%	1.14 [1.03, 1.27]	
Wokołorczyk 2008	498	970	1817	3820	20.0%	1.16 [1.01, 1.34]	
Subtotal (95% CI)		5650		19368	100.0%	**1.08 [1.02, 1.16]**	
Total events	2955		9854				
Heterogenity: Chi²=4.40, df=3 (P=0.22); I²=32%							
Test for overall effect: Z=2.45 (P=0.01)							
2 GG *vs.* TT							
Akdi 2011	114	202	142	259	12.5%	1.07 [0.74, 1.55]	
Cipollini 2013	292	570	307	597	33.7%	0.99 [0.79, 1.25]	
Jones 2012	241	405	1662	3103	35.8%	1.27 [1.03, 1.57]	
Wokołorczyk 2008	122	231	420	933	18.1%	1.37 [1.02, 1.82]	
Subtotal (95% CI)		1408		4892	100.0%	**1.17 [1.03, 1.33]**	
Total events	769		2531				
Heterogenity: Chi²=3.96, df=3 (P=0.27); I²=24%							
Test for overall effect: Z=2.41 (P=0.02)							
3 GG+GT *vs.* TT							
Akdi 2011	301	389	346	463	11.3%	1.16 [0.84, 1.59]	
Cipollini 2013	922	1200	906	1196	33.3%	1.06 [0.88, 1.28]	
Jones 2012	587	751	4674	6115	35.3%	1.10 [0.92, 1.32]	
Wokołorczyk 2008	376	485	1397	1910	20.1%	1.27 [1.00, 1.60]	
Subtotal (95% CI)		2825		9684	100.0%	**1.13 [1.01, 1.26]**	
Total events	2186		7323				
Heterogenity: Chi²=1.41, df=3 (P=0.70); I²=0%							
Test for overall effect: Z=2.20 (P=0.03)							
4 GG *vs.* GT+TT							
Akdi 2011	114	389	142	463	13.1%	0.94 [0.70, 1.26]	
Cipollini 2013	292	1200	307	1196	33.3%	0.93 [0.77, 1.12]	
Jones 2012	241	751	1662	6115	35.3%	1.27 [1.08, 1.49]	
Wokołorczyk 2008	122	485	420	1910	18.2%	1.19 [0.95, 1.50]	
Subtotal (95% CI)		2825		9684	100.0%	**1.10 [0.99, 1.22]**	
Total events	769		2531				
Heterogenity: Chi²=7.57, df=3 (P=0.06); I²=60%							
Test for overall effect: Z=1.80 (P=0.07)							
5 GT *vs.* TT							
Akdi 2011	187	275	204	321	10.8%	1.22 [0.87, 1.71]	
Cipollini 2013	630	908	599	889	33.1%	1.10 [0.90, 1.34]	
Jones 2012	346	510	3012	4453	35.6%	1.01 [0.83, 1.23]	
Wokołorczyk 2008	254	363	977	1490	20.5%	1.22 [0.95, 1.57]	
Subtotal (95% CI)		2056		7153	100.0%	**1.10 [0.99, 1.24]**	
Total events	1417		4792				
Heterogenity: Chi²=1.79, df=3 (P=0.62); I²=0%							
Test for overall effect: Z=1.71 (P=0.09)							

Figure 2. Meta-analysis for the association between rs6983267 polymorphisms and thyroid cancer risk.

different using the χ² statistic (P<0.01), which should affect the results. Furthermore, small sample size or prevalence of TC or some environmental factors may have affected the results. When other environmental risk factors prevail, the small-size effect of rs6983267 may be obscured. Therefore, it is not surprising that the associations between rs6983267 genotype

and cancer risk were detectable in populations with low incidences of DTC (in Poland and the United Kingdom, the age-standardized rates are 4.1 and 3.8 cases out of 100 000 population, respectively), whereas lack of association was found in Texans and Italians, where the incidence is much higher (10.8 and 13.5, respectively) [10]. To eliminate the effects of

potential confounding factors, it might be reasonable to perform subgroup analyses according allele frequency distribution, ethnic background, incidence of TC, and other environmental risk factors. However, because of the limited number of included studies, we could not do this.

The pseudogene of POU5F1 is the nearest gene to rs6983267 located in the 8q24 chromosomal gene-poor region (gene desert). POU5F1 encodes a transcription factor of Octamer-binding transcription factor (OCT4). The Oct4 gene, which is a key regulator of stem cell pluripotency, is specifically expressed in embryonic stem cells but can also be detected in adult stem cells [24]. In addition, recent studies have demonstrated that the Oct4 gene is expressed in several human cancer tissues and derived cell lines, including thyroid cancer [25–27]. Therefore, it is possible to hypothesize that the Oct4 gene might play a critical role in tumorigenesis, although the mechanistic role in cancer is unknown. Tomlinson et al. [28] detected differences in Oct4 gene expression according to rs6983267 status in colorectal cancer, but failed to find a clear association. However, there has no such study on thyroid cancer until now, and this requires further study. The nearest protein-coding gene, MYC, locates ~335 kb downstream from rs6983267. Some studies [29, 30] have suggested that this locus is a long-range cis-regulatory enhancer element for the MYC gene and is involved in regulating MYC expression. However, other studies [28] did not detect an unambiguous correlation between rs6983267 genotype and MYC expression. Therefore, the plausible regulatory role of this locus in MYC gene function needs further study.

Several potential limitations of our meta-analysis should be acknowledged. First, although the funnel plot did not detected significant publication bias, potential publication bias is probably present because we did not include unpublished studies and non-English language published studies in the meta-analysis. Second, the cancer cases in the included studies were not uniformly defined, and the data were not adjusted by other factors, such as age, sex, and lifestyle, because of the lack of detailed individual data. Third, there might be a selection bias because races/cultures of only 4 European regions were considered and genetic differences are likely to exist.

Conclusions

The rs6983267 G>T polymorphism in the 8q24 region might be a risk factor for thyroid cancer. However, the limitations and the small total sample size in our study make it impossible to draw a final conclusion. Therefore, further research with larger sample sizes and full consideration of confounding risk factors is needed to confirm or modify our conclusions. Potential gene-gene association should be included in future studies.

Declaration of interest

None.

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