The 8q24 rs6983267G variant is associated with increased thyroid cancer risk

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Abstract

The G allele of the rs6983267 single-nucleotide polymorphism, located on chromosome 8q24, has been associated with increased risk of several cancer types. The association between rs6983267G and thyroid cancer (TC) has been tested in different populations, mostly of European ancestry, and has led to inconclusive results. While significant associations have been reported in the British and Polish populations, no association has been detected in populations from Spain, Italy and the USA. To further investigate the role of rs6983267G in TC susceptibility, we evaluated rs6983267 genotypes in three populations of different continental ancestry (British Isles, Colombia and Japan), providing a total of 3067 cases and 8575 controls. We detected significant associations between rs6983267G and TC in the British Isles (odds ratio (OR) = 1.19, 95% CI: 1.11–1.27, P = 4.03 × 10⁻⁷), Japan (OR = 1.20, 95% CI: 1.03–1.41, P = 0.022) and a borderline significant association of similar effect direction and size in Colombia (OR = 1.19, 95% CI: 0.99–1.44, P = 0.069). A meta-analysis of our multi-ethnic study and previously published non-overlapping datasets, which included a total of 5484 cases and 12 594 controls, confirmed the association between rs6983267G and TC (P = 1.23 × 10⁻⁷, OR = 1.13, 95% CI: 1.08–1.18). Our results therefore support the notion that rs6983267G is a bona fide TC risk variant that increases the risk of disease by ~13%.
Introduction

Thyroid cancer (TC) incidence is increasing worldwide and is becoming an epidemic malignancy (Ferlay et al. 2015). In the USA, for example, where the incidence of most common malignancies has been decreasing, the annual percentage change of incidence increase for TC is >5%, the highest among all cancers (Edwards et al. 2014). If the current rate of increase in incidence continues, TC will become the fourth most common cancer in the USA by 2030 and the third most commonly diagnosed malignancy among American women by 2017 (Rahib et al. 2014). Although TC shows a sexual disparity and affects more women than men, the increasing incidence is affecting both sexes (Edwards et al. 2014). While over-diagnosis may partially explain such increases in incidence, it does not fully account for such a dramatic change. Other elements that may contribute to these changes in incidence could include unaccounted changes in lifestyle and environmental factors that could interact with genetic risk variants to mediate TC risk (Pellegriti et al. 2013).

Interestingly, TC risk has a strong familial component and first-degree relatives of TC patients have up to eight times higher risk of developing TC than the general population (Goldgar et al. 1994, Hemminki & Li 2003). This suggests that genetic elements play a major role in TC risk. The genetics of TC, however, remain relatively unexplored, but increasing evidence suggests that multiple low penetrance genetic variants, rather than a few high penetrance genes, can better explain the risk of TC (Landa & Robledo 2011). Genome-wide association (GWA) studies in European populations have identified five low penetrance TC variants, including rs965513 on 9q22, rs944289 on 1q43, rs966423 on 2q35, rs2439302 on 8p12 and rs116909374 on 14q13.3 (Gudmundsson et al. 2009, 2012, Takahashi et al. 2010). Candidate studies have also been used to investigate TC genetics. For example, Landa et al. (2009) independently identified a second risk variant on chromosome 9q22 located in 5' UTR region of thyroid specific transcription factor FOXE1, which showed moderate linkage disequilibrium with rs965513, one of the variants identified by GWA studies. In another candidate study, rs6983267, a multi-cancer single-nucleotide polymorphism (SNP) was tested for association with TC in the Polish population and was found to be significantly associated with increased TC risk (Wokoloczyk et al. 2008). However, subsequent studies testing the association between rs6983267 and TC in other populations have reported conflicting results. For example, we found that rs6983267G was associated with TC in the UK population and that it increased the association with disease using both recessive and allelic models (Jones et al. 2012). Studies in the USA, Italian and Spanish cohorts have not, however, been able to replicate an association between this 8q24 variant and TC (Akdi et al. 2011, Neta et al. 2012, Cipollini et al. 2013).

To further assess the role of rs6983267G in TC risk, we genotyped rs6983267 in a large and multi-ethnic sample set that included 3067 cases and 8575 controls of European, Hispanic and Japanese ancestry. Our results indicate that rs6983267 is indeed associated with increased risk of all the three populations examined in the study. Interestingly, the risk conferred by this variant seems to be stronger for larger tumors. Additionally, a meta-analysis that included all previously published data also confirmed a significant association between the rs6983267G allele and TC and suggests that this variant increases disease risk by ~13%.

Materials and methods

Study samples

British Isles study We examined 2338 patients with histologically confirmed non-medullary TC that were recruited through thyroid cancer genetics UK and Ireland (TCUKIN) study, a multi-center study that recruited 2172 TC patients in the UK and 166 patients in the Republic of Ireland through TC clinics. These samples include data from 768 previously reported cases (Jones et al. 2012). All patients had White/Northern European ancestry, completed a questionnaire and donated a blood sample that was used for isolation of DNA. As controls, we genotyped 189 cancer-free Irish individuals from Galway and used previously published data from 6067 cancer-free controls from the COloRectal Gene Identification study (Tomlinson et al. 2007) and participants from National Blood Donor service and 1958 Birth Cohort studies (Jones et al. 2012). The TCUKIN protocols were approved by Southampton and South West Hampshire Research Ethics Committee and by National University of Ireland, Galway, Ireland.

Colombian study We examined 281 incident TC cases that were recruited in a multi-center study in the Colombian cities of Medellin, Ibague and Neiva, all of which are populations of Hispanic ancestry.
(Carvajal-Carmona et al. 2000, 2003, Bedoya et al. 2006). Cases were eligible if they were diagnosed with a histopathologically verified non-medullary TC and had verified local origin through an in-person genealogical questionnaire. For this study, we have also near complete information on tumor size for all the patients who were classified as having either micro-carcinomas (tumor <1 cm in size) or macro-carcinomas (tumors of ≥1 cm in size). Population- and gender-matched controls included 899 cancer-free individuals, recruited in the same centers, and who did not have a family history of cancer in first-degree relatives. The Ethics Committees from University of Tolima (Ibagué), Hospital Federico Lleras Acosta (Ibagué), Hospital Fernando Moncaleano (Neiva) and Hospital Pablo Tobon Uribe (Medellin) approved the research protocol used in the Colombian study.

Japanese study Four hundred and forty-eight patients with sporadic papillary TC (PTC) were recruited from Kuma Hospital (Kobe, Japan) with confirmed histological diagnosis performed by a thyroid pathologist. At Kyoto University (Kyoto, Japan), 1420 controls were collected. Neither cases nor controls reported a history of exposure to radiation. The Ethics Committees of Nagasaki University, Kuma Hospital, and Kyoto University approved the study protocol.

Genotyping

The British and Colombian samples were genotyped with KASP genotyping chemistry using conditions and probes described previously (Jones et al. 2012). British control genotype data was available from 6067 participants from the NBS, BC58 and CORGI studies and was obtained as reported by Jones et al. (2012). Japanese and TCUKIN Irish cases and controls were genotyped using a pre-designed and functionally tested custom TaqMan primer/probe set, C_29086771_20 (Applied Biosystems). Genotyping call rates for the Colombian, British Isles and Japanese study were all >95% and none of the studies had Hardy–Weinberg $P$ values >0.05.

Statistical analysis

Association statistics were obtained using logistic regression methods implemented in PLINK and R (Purcell et al. 2007). Meta-analyses and heterogeneity were calculated using Peto’s method of pools of odds ratios (ORs) using STATA (Yusuf et al. 1985). The $I^2$ statistic was used to access the heterogeneity between studies as previously shown (Yusuf et al. 1985, Higgins & Thompson 2002, Carvajal-Carmona et al. 2011, Cancer Genome Atlas Research Network 2014). All $P$ values were two-sided.

Results

Association between rs6983267G and TC risk in the UK, Colombia and Japan

We analyzed rs6983267 genotype data from a total of 3067 cases and 8575 controls from the British Isles, Colombia and Japan. Genotype and allele counts, ORs and allelic $P$ values in each one of these three populations are shown in Table 1. We detected consistent and significant associations between rs6983267G and TC in the British Isles ($P=4.03 \times 10^{-7}$; OR =1.19, 95% CI: 1.11–1.27, Fig. 1), Japan ($P=0.022$; OR =1.20, 95% CI: 1.03–1.41) and a borderline significant association of similar effect size and direction in Colombia ($P=0.069$; OR =1.19, 95% CI: 0.99–1.44). During the preparation of this manuscript,

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotypes/ risk allele</th>
<th>No. of cases (frequency)</th>
<th>No. of controls (frequency)</th>
<th>Odds ratio (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
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<td>TT</td>
<td>539 (0.231)</td>
<td>1709 (0.273)</td>
<td>Reference</td>
<td></td>
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<tr>
<td></td>
<td>GT</td>
<td>1150 (0.492)</td>
<td>3087 (0.493)</td>
<td>1.18 (1.05–1.33)</td>
<td>5.74 \times 10^{-3}</td>
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<tr>
<td></td>
<td>GG</td>
<td>649 (0.278)</td>
<td>1460 (0.233)</td>
<td>1.41 (1.23–1.61)</td>
<td>5.06 \times 10^{-7}</td>
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<tr>
<td></td>
<td>G allele</td>
<td>2448 (0.524)</td>
<td>6007 (0.480)</td>
<td>1.19 (1.11–1.27)</td>
<td>4.03 \times 10^{-7}</td>
</tr>
<tr>
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<td>183 (0.204)</td>
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<tr>
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<td>1.48 (0.98–2.22)</td>
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<td>G allele</td>
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<td>961 (0.534)</td>
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<tr>
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<td>175 (0.390)</td>
<td>645 (0.454)</td>
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<td>1.28 (1.02–1.61)</td>
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<td>172 (0.121)</td>
<td>1.35 (0.97–1.88)</td>
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<td>947 (0.333)</td>
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a subset of the Japanese case data and a much larger control sample that included imputed genotype data (n=2759) were reported in another study, which found a similar and consistent effect size between rs6083267G and TC risk in Japan (OR=1.14) (Rogounovitch et al. 2015). Consistent with our previous report (Jones et al. 2012), rs6983267G was associated with TC risk using a recessive model in the British Isles (Supplementary Table 1, see section on supplementary data given at the end of this article). A recessive model, however, was not significant in Colombia or in Japan (Supplementary Table 1). These consistent associations in these three very distinct ethnic populations therefore strongly suggest that the common rs6983267G allele represents a TC risk variant.

**Association between rs6983267G and risk in histological subtypes of TC**

Histologically, TC can be divided into three main subtypes. PTC is the most common form, comprising of ~80% of all cases followed by the follicular TC (FTC) that comprises 10–20% of TC cases and by the rarer follicular variant of PTC (FV-PTC), the latter which has been traditionally classified as PTC (Carling & Udelsman 2014). However, the recent TC genomic characterization carried out by The Cancer Genome Atlas (TCGA) study suggests that FV-PTC is molecularly very distinct from PTC and should be grouped with FTC (Cancer Genome Atlas Research Network 2014). To test if rs6983267G is associated with increased risk of a specific histological TC subtype, we classified TC cases from British Isles and Colombia (where histopathological data was available in 1951 cases and 281 cases respectively) into PTC and FV + FTC. All Japanese cases were of PTC histology. We detected consistent and significant associations between rs6983267G and both the PTC (PTC, \( P=5.5 \times 10^{-5} \), OR = 1.20, Table 2) and FV+FTC subtypes (\( P=5.50 \times 10^{-4} \), OR = 1.21, Table 2) in the British Isles. In the Colombian population, we detected associations with both the PTC (OR = 1.21, Table 2) and FV+FTC (OR = 1.15, Table 2) subtypes with similar effect sizes. However, the P values were not significant, likely due to the smaller sample size of the study. Cases-only analyses failed to detect a significant differential effect of rs6983267G on TC subtypes (PTC vs FV+FTC, \( P>0.70 \) for all populations, data not shown). Our results therefore suggest that rs6983256G is a TC risk variant that is not specifically associated with any particular TC subtype. This finding is consistent with previous TC GWA studies, which also have failed to detect SNP associations with specific TC subtypes (Gudmundsson et al. 2009).

**Associations between rs6983267G in micro- and macro-carcinomas**

To test whether tumor size influenced the risk associated with rs6983267G, we evaluated the association separately for micro- and macro-carcinomas in the Colombian study where details of tumor size for most patients were readily available. Interestingly, we detected a significant association between rs6983267G and TC when only larger tumors were analyzed (\( P=0.018 \), OR = 1.33, 95% CI: 1.05–1.69, Table 3) whereas, no significant association was observed with micro-carcinomas (\( P=0.733 \), OR = 1.06, 95% CI: 0.75–1.50, Table 3). These data, although obtained in a limited number of cases, suggests that rs6983267G might increase the risk of tumor progression rather than initiation or that rs6983267G could be associated with the risk of more aggressive tumors. Although further studies should assess this finding in more detail and in a significantly higher patient sample size, our data in these small set of 235 patients are consistent with our previous study in colorectal adenomas, a risk factor and an intermediate phenotype for colorectal cancer (Carvajal-Carmona 2010) where we showed that known colorectal cancer SNPs acted at different stages of tumorigenesis, some affecting cancer initiation and others affecting cancer progression (Carvajal-Carmona et al. 2013).
Meta-analysis with previously published data

To further assess the association between TC risk and rs6983267G, we performed meta-analysis of our multi-ethnic study and all previously published data from populations of European ancestry from the USA, Spain, Italy and Poland (Wokolorczyk et al. 2008, Akdi et al. 2011, Cipollini et al. 2013). Supplementary Table 2 (see section on supplementary data given at the end of this article) shows previously reported data in these latter populations. Our meta-analyses detected, as expected, moderate heterogeneity ($I^2=52\%$, $P=0.053$, Fig. 1) likely due to the great variation in risk allele frequencies (RAF) across all three continental populations (RAF Colombia = 0.534; RAF Europeans = 0.483–0.527 and RAF Japan = 0.333, Table 1 and Supplementary Tables 2 and 3). Despite this heterogeneity, our large meta-analyses of these 5484 TC cases and 12,594 controls suggest that rs6983767G does increase the risk of TC by $\sim13\%$. ($P=1.23\times10^{-7}$, OR = 1.13, 95% CI: 1.08–1.18, Fig. 1). This finding therefore further suggests that rs6983267G represents a bona fide TC allele.

Discussion

TC is the most common endocrine malignancy and its incidence is increasing at an alarming rate in most populations (Ferlay et al. 2015). Studies investigating its causes are therefore needed if we want to reduce the health care burden associated with this increasingly common malignancy. Interestingly, several epidemiological studies suggest that TC is one of the most familial malignancies and one of the few where the genetic risk, measured in terms of heritability (53%), is larger than the environmental risk (Weires et al. 2011). Therefore, dissecting the genetic etiology of TC represents an initial step in further understanding disease biology and to design optimal preventive and therapeutic programs for this endocrine cancer.

The chromosome 8q24 rs6983267G variant is perhaps the most important cancer risk allele as it has been associated with increased risk of cancers of the prostate, colon, ovary and tumors at several other sites (Haiman et al. 2007a, Tomlinson et al. 2007, Yeager et al. 2007, Zanke et al. 2007, Wokolorczyk et al. 2008). The precise function of this locus is still under investigation as it is located in a gene desert, with the nearest genes being the OCT4 related POU5F1P1 (also known as POU5F1B) gene and the oncogene MYC (Supplementary Fig. 1, see section on supplementary data given at the end of this article).
Over-expression of MYC has been detected in a variety of different cancers including TC (Yamashita et al. 1986). While several studies have shown that this region has enhancer activity and shows long-rang interaction with MYC, a clear correlation between rs6983267G and MYC or POU5F1P1 expression is not yet clearly established (Pomerantz et al. 2009, Tuupanen et al. 2009). A recent study demonstrated transcription of a long non-coding RNA CARLo across 8q24, promoter of which interacted with enhancer encompassing rs6983267, and was found to function in cell-cycle regulation and tumor development, thus highlighting the complex biological function of this region (Kim et al. 2014). Interestingly, the frequency of rs6983267G is high in most populations ranging from 30% to as high as 85% (Supplementary Table 3, Haiman et al. 2007b) and thus the contribution of this allele on cancer burden is considerable and needs to be assessed further with regards to cancer risk at different organ sites. The aim of this study was to access the role of the rs6983267G variant on TC risk in a multi-ethnic sample and to further investigate whether the multi-cancer rs6983267G allele was a risk factor for this common endocrine malignancy. Our data in three different continental populations indicate that rs6983267G is associated with increased risk of TC. The meta-analyses with four previous reports in populations of European descent further suggest that rs6983267G is indeed a bona fide TC risk variant. We provide strong evidence suggesting that having a copy of this allele increases the risk of TC by ~13%.

Few previously published studies in the European-American, Spanish and Italian populations did not find significant associations between rs6983267G and TC (Akdi et al. 2011, Neta et al. 2012, Cipollini et al. 2013). One of the possible reasons that could explain why these studies failed to find an association could have been their limited statistical power to convincingly exclude an effect of rs6983267G on TC. Based on the results from our meta-analyses, to detect an OR of 1.13 with an 80% power at \( P<0.05 \), over 1800 cases and a similar number of controls would be required. None of the previous studies that failed to detect associations with rs6983767G had sample sizes near such numbers (see Supplementary Table 3 for more details). Other than differences in the statistical power to replicate or to exclude an effect, a further potentially important factor explaining differences with some of the previous studies could be the TC genetic heterogeneity, where complex and population-specific interactions between genetic and environmental risk factors play a role in its etiology (Vigneri et al. 2015).

The past decades have seen an epidemic rise in TC incidence, faster than tumors at any other site (Bray et al. 2013, Ferlay et al. 2013, 2015). Interestingly, TC incidence also greatly varies in different populations. For example, the USA and Italy now report among the highest TC incidence, which is three to four times higher than reported in Japan, Colombia and other European countries such as the UK or Poland (Supplementary Table 3). The majority of the increase in the incidence (87%) can be explained by micro-carcinomas, probably due to increased medical surveillance and access to diagnostic techniques such as ultrasound and fine needle aspiration cytology (Davies & Welch 2006, Ahn et al. 2014, Davies & Welch 2014). As observed in our Colombian study, where tumor size information was readily available for most cases, only large tumors showed an association with rs6983267G. This finding, although obtained in only 235 cases, is consistent with a recent report from Japan, that used samples that overlapped with the present study, and that failed to detect associations between rs6983267G and pre-malignant lesions (follicular adenomas) in the thyroid (Rogounovitch et al. 2015). Although more detailed studies with larger sample size are needed to further confirm this observation, our preliminary data in a small patient population from Colombia is indicative of a stronger association with larger tumors. This suggests that rs6983267G could play a more important role in cancer progression rather than in cancer initiation. Therefore, it could be plausible that studies carried out in populations or sample sets with a higher proportion of pre-malignant lesions or of micro-carcinomas might fail to detect associations with disease progression SNPs. Over-diagnosis in such populations could lead to an increased chance of including phenocopies or less genetically-influenced cases, thus further decreasing the power to detect associations between SNPs and disease.

In summary, our study, which is one of the largest and most ethnically diverse association studies carried out for TC genetics to date, suggests that rs6983267G, when
analyzed individually in populations of different ethnicity and in meta-analysis, represents a risk factor for TC. Based on our meta-analyses results of rs6983267 genotype data in 5484 TC cases and 12,594 controls which detected a significant association with TC, we suggest that variation at this locus should be included in future risk assessment programs that include genetic information.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-15-0081.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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