Strong Association of Chromosome 1p12 Loci with Thyroid Cancer Susceptibility

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Abstract

Several genes directly related to thyroid cancer development have been described; nevertheless, the genetic pathways of this tumorigenesis process are unknown. Together with environmental factors, susceptibility genes could have an important role in thyroid cancer. Our previous studies suggest that the chromosome 1p12-13 is related to thyroid cancer incidence. Here, we extend the analysis with a case-control association study in a Spanish population. Thus, six single-nucleotide polymorphisms were genotyped, covering 2.4 Mb of the 1p12-13 region. A statistically significant association between thyroid cancer incidence and the rs2145418 and rs4658973 polymorphisms was found ($P < 0.0001$). No association was detected for the other four polymorphisms studied. The rs2145418 marker showed a significant odds ratio of 5.0 [95% confidence interval (95% CI), 2.85-8.83] and 9.2 (95% CI, 4.50-21.6) for heterozygous and homozygous G-variant alleles, respectively. For rs4658973, the odds ratios were 0.40 (95% CI, 0.26-0.62) and 0.07 (95% CI, 0.03-0.18) for heterozygous and homozygous G-variant alleles, respectively. These markers map into the 1p12 region, and no linkage disequilibrium was found between them, indicating an independent relation of these polymorphisms with thyroid cancer susceptibility. Our data provide evidence of a strong association of the chromosome 1p12 with thyroid cancer risk, and it is the first study describing susceptibility loci for thyroid cancer in this region. (Cancer Epidemiol Biomarkers Prev 2008;17(6):1499–504)

Introduction

Thyroid cancer is the most frequent endocrine cancer with familial and sporadic forms, the latter being the most common type of thyroid cancer (1). Genetic factors directly related to thyroid tumorigenesis have been reported (2, 3), but the genetic pathways of such processes remain to be established (3, 4). Together with the genetic effects, the role of environmental factors in thyroid cancer development is well known, ionizing radiation being the best recognized risk factor for this pathology (5, 6). Nevertheless, the etiology of thyroid cancer is still unknown. In general, it is believed that susceptibility genetic factors are crucial in the genomics of cancer development; thus, association studies aiming to identify susceptibility genes for cancer are taking important relevance. This type of study has recently emerged for thyroid cancer (7-12), although no specific genetic factor for thyroid cancer susceptibility has yet been described. In a previous study, we have reported that the chromosome 1p12-13is related to thyroid cancer susceptibility (13). Several studies also indicate that this region undergoes many aberrations in different types of cancer (14-17), which would suggest a certain role in cancer incidence. Here, we report the localization of susceptibility factors to thyroid cancer in this region. We have carried out a case-control study in a Spanish population analyzing six single-nucleotide polymorphisms covering 2.4 Mb of the chromosome 1p12-13 region to localize susceptibility factors. We found that, in the studied population, the single-nucleotide polymorphisms rs2145418 and rs4658973, which are separated by 377 kb, have a strong association ($P < 0.0001$) with thyroid cancer.

Materials and Methods

Subjects and DNA Isolation. In this study, two populations of unrelated Spanish subjects were genotyped. Blood samples were collected from 202 healthy individuals (117 women and 85 men; mean age, 41.2 ± 13.2 years) and from 227 thyroid cancer patients (167 women and 60 men; mean age, 43.5 ± 14.6 years) from the Nuclear Medicine Service at the University Hospital Vall d'Hebron (Barcelona). Tumors of these patients were classified as papillary (171), follicular (39), or Hürthle cell (6) carcinomas. This information was not available for 11 individuals at the moment of the study, and these were considered as unclassified. All individuals gave informed consent, and clearance from the ethical committee of our institutions was obtained.

DNA isolation was done using a standard phenol-chloroform method and 30 to 100 μL of Tris-EDTA [10 mmol/L Tris; 0.2 mmol/L EDTA (pH 7.5)].
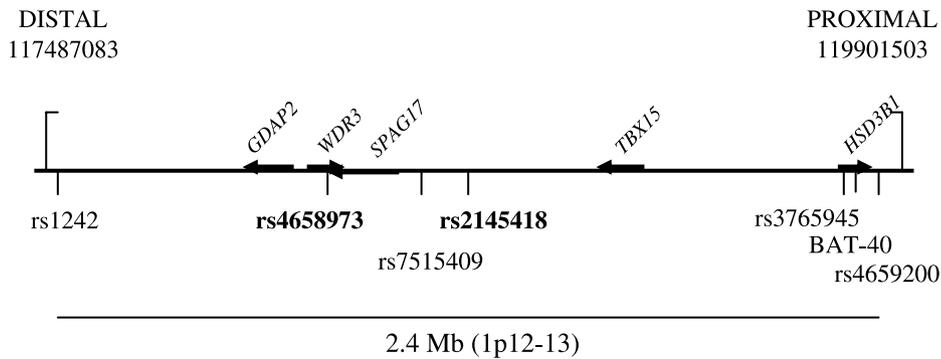
Figure 1. Map position of the six studied single-nucleotide polymorphisms at chromosome 1p12-13 and relative to the BAT-40 marker. Single-nucleotide polymorphisms associated with thyroid cancer susceptibility are indicated in bold.

Genotyping. Case and control populations were genotyped by analyzing six single-nucleotide polymorphisms markers localized in the 1p12-13 region: rs4659200, rs3765945, rs2145418, rs7515409, rs4658973, and rs1241. The selection of the single-nucleotide polymorphisms was based on the information available in the public databases, on allele frequency (common variants; minor allele frequency, >0.2), and on the possibility of PCR-RFLP analysis. The six single-nucleotide polymorphisms were chosen to cover a region of 2.4 Mb of the chromosome 1p12-13, and none of the selected single-nucleotide polymorphisms was considered haplotype tagged single-nucleotide polymorphisms by the HapMap database. Relative map position of these markers is shown in Fig. 1.

Genotypes were generated by RFLP after PCR amplification. The rs7515409 and rs4658973 markers were genotyped on 202 control and 227 patient samples. From all originally collected samples, a reduced number was available in the subsequent analysis of the rs4659200, rs3765945, rs2145418, and rs1241 single-nucleotide polymorphisms; therefore, 136 control and 201 patient samples were only used to genotype these markers. Taking into consideration the variant allele frequencies (range, 0.24-0.48) of these polymorphisms, the sample size of the study was sufficient to detect odds ratios of 2.2 and 1.9, respectively, with $\alpha = 0.05$ and a power of 95% (G-Power software; ref. 18).

Primers used to amplify each single-nucleotide polymorphism, as well as the PCR product lengths, the restriction enzymes used, and the RFLP fragments are shown in Table 1.

PCRs were carried out in a final volume of 25 μL using 100 ng of DNA in 1× PCR buffer (10 mmol/L of Tris-HCl, 50 mmol/L of KCl, and 0.1% Triton X-100), 2.5 mmol/L of $MgCl_2$, 0.2 mmol/L of each deoxynucleotide triphosphate, 0.1 μmol/L of each primer, and 0.75 U of *Taq* DNA polymerase (Promega). Amplifications were as follows: an initial denaturing step at 94°C for 4 min, 30 cycles at 94°C for 30 s, 54°C for 40 s, 72°C for 1 min, and a final step at 72°C for 4 min. PCR products were then digested using the restriction enzymes *Afl*III (New England Biolabs), *Sap*I (New England Biolabs), *Acs*I (Roche), *Bsr*I (New England Biolabs), *Taq*I (Roche), and *Nla*III (New England Biolabs) for rs4659200, rs3765945, rs2145418, rs7515409, rs4658973, and rs1241, respectively. The digestion products were resolved on 2.5% agarose gels. Genotyping errors were discarded by successful duplicate analysis of 10 samples for each single-nucleotide polymorphism. In addition, an alternative genotyping method was also done in 117 control and 114 patient samples using the MassArray technique (Sequenom, Inc.) to genotype the rs2145418 and rs4658973 markers. RFLP and MassArray gave an identical genotype profile, in which sample errors were not detected.

Statistical Analysis. Allele frequencies for the six single-nucleotide polymorphisms were calculated from the genotype frequencies and compared by the χ^2 test or the Armitage's trend test, when Hardy-Weinberg equilibrium failed (that is, rs2145418 and rs1241). Hardy-Weinberg equilibrium was tested in the control population. The degree of pairwise linkage disequilibrium between markers was expressed as D' and r^2 values.

Table 1. PCR amplification primers and restriction enzymes used for genotyping six single-nucleotide polymorphisms of the 1p12 region

Single-nucleotide polymorphism	Primer sequence	Product size (bp)	Restriction enzyme	Size of fragments (bp)
rs4659200	F 5′-TGATTCCAGCCTCTCATTAG-3′ R 5′-GTGTTACAGCCAATGGAGTG-3′	374	*Afl*III(T)	173 + 201
rs3765945	F 5′-CAATACCTCTAGGCTGAGCA-3′ R 5′-CAAAACAATTCCCTGTCCTC-3′	315	*Sap*I(C)	153 + 162
rs2145418	F 5′-GAATGGCTGGTGAGGAAT-3′ R 5′-TGTTCATTGCAGCACTATTC-3′	657	*Acs*I(T)	168 + 489
rs7515409	F 5′-GGCTGATTAGCTCCAAGTTC-3′ R 5′-GCATACTCCTCAGTGGCAGT-3′	536	*Taq*I(G)	240 + 297
rs4658973	F 5′-GGGACACTTGAGACCAAAAG-3′ R 5′-TCAAATGGGATTACAAACCT-3′	341	*Bsr*I(T)	142 + 199
rs1241	F 5′-AGCCACACTGGTAATTGATA-3′ R 5′-TTACAACCTGGAGATAGCTG-3′	415	*Nla*III(C)	170 + 245

Abbreviations: F, forward; R, reverse.

Table 2. Allele frequencies of the six studied single-nucleotide polymorphisms

Single-nucleotide polymorphism	Nucleotide change	Controls (n)	Patients (n)	χ^2
rs4659200	C>T	0.39 (136)	0.35 (200)	0.28
rs3765945	T>C	0.33 (136)	0.35 (199)	0.60
rs2145418	T>G	0.24 (136)	0.57 (197)	<0.0001*
rs7515409	T>C	0.46 (197)	0.46 (222)	0.86
rs4658973	T>G	0.48 (194)	0.26 (214)	<0.0001
rs1241	T>C	0.33 (135)	0.35 (201)	0.49*

NOTE: Frequencies of the less represented allele are shown for each single-nucleotide polymorphism.
*Compared by the Armitage's trend test.

Although both coefficients represent the most common measures of linkage disequilibrium, the use of r^2 is recommended in association studies (19).

Association between single-nucleotide polymorphisms and thyroid cancer susceptibility was calculated by the odds ratio and 95% confidence intervals (95% CI) using logistic regression analyses adjusted for age, sex, and alcohol and smoking habits.

We assumed a model of multiplicative allelic effect (codominant model). All analyses were done with a 5% level of significance using the SNP.stats software.[4]

Results

We previously reported that the chromosome 1p12-13 was associated with thyroid cancer susceptibility in a case-control study using the microsatellite BAT-40 marker (13). In the present study, we have conducted a fine mapping of the susceptibility loci in this region by extending the analysis to an average distance of 2.4 Mb. We have used six additional polymorphic markers to examine for any association with an increased risk for thyroid cancer. As shown in Fig. 1, rs4659200 and rs3765945 are surrounding our marker of reference, BAT-40 (proximal extreme of the 2.4-Mb region); rs2145418, rs7515409, and rs4658973 map to the middle of the analyzed region; and rs1241 is located on the distal extreme of this region.

Because of the different frequency of females between our control (58%) and patient (74%) populations, for each single-nucleotide polymorphism, the genotype distribution about gender was analyzed before doing the association analysis, but no significant difference was found (data not shown). Consequently, the different proportion of females between control and patient groups does not influence our association analysis.

Single-nucleotide polymorphisms, nucleotide changes, and allele frequencies in cases and controls are shown in Table 2. In the control population, the observed genotype frequencies did not differ from those expected from the Hardy-Weinberg equilibrium for the rs4659200, rs3765945, rs7515409, and rs4658973 polymorphisms. However, for rs1241 and rs2145418, significant deviations from Hardy-Weinberg equilibrium were observed ($P = 0.007$ and $P = 0.005$, respectively). In these cases, genotyping errors were discarded as being the cause of the Hardy-Weinberg deviations because nonerrors were

detected by duplicate genotype analysis (see Materials and Methods). Appropriate correction for these deviations was then used when comparing allele frequencies between cases and controls for these two polymorphisms (Armitage's trend test), as shown in Table 2. On the other hand, we checked the pairwise linkage disequilibrium coefficients D' and r^2, and we did not find strong linkage disequilibrium between any combination of markers (Table 3), indicating an independent transmission pattern of inheritance. Even those markers with near position showed weak association, for example, rs4659200 and rs3765945 that are 48.5 kb apart and present a weak association ($D' = 0.35$, $r^2 = 0.04$).

As shown in Table 2, significant differences between control and patient groups were found with respect to the allele frequencies of the rs2145418 and rs4658973 single-nucleotide polymorphisms. The G variant of rs2145418 is overrepresented in patients ($P < 0.0001$), whereas the G variant of rs4658973 is underrepresented in this cohort ($P < 0.0001$). Genotype distribution of the six single-nucleotide polymorphisms in the control and patient cohorts, and their odds ratios are shown in Table 4. We want to point out that no difference was found between the crude odds ratio and the adjusted odds ratio for age, sex, alcohol, and tobacco, which discard these features acting as confounding factors in this study. Therefore, the crude values of the odds ratio were used to assess the association between thyroid cancer and polymorphic variants. Significant odds ratios for the rs2145418 and rs4658973 polymorphisms were found ($P < 0.0001$ for each marker; see Table 4), which indicates a strong association between thyroid cancer and these single-nucleotide polymorphisms. No association was detected for the other four polymorphisms studied.

Association between thyroid cancer and the G-variant allele of the rs2145418 was shown by the significant odds ratios found, with values of 5.0 for heterozygous carriers (95% CI, 2.85-8.83; $P < 0.0001$) and of 9.2 for the homozygous (95% CI, 4.50-21.6; $P < 0.0001$). Therefore, carrying only one G allele is sufficient to increase 5-fold the risk for thyroid cancer. For the rs4658973 marker, the T allele is associated with thyroid cancer, which provides a second marker for thyroid cancer susceptibility. In this case, the T variant is the frequent allele in the control population (T, 0.55; G, 0.45), being even more frequent in patients (T, 0.73; G, 0.26). We used the homozygous carriers of the frequent allele as the reference genotype to calculate the odds ratio (see Table 4); therefore, in the case of the rs4658973 marker, the odds ratios for the GT and GG genotypes take the inverse value that is inferior than 1, that is, 0.40 (95% CI, 0.26-0.62; $P < 0.0001$) and

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[4] http://bioinfo.iconcologia.net/snpstats/

Table 3. Pairwise linkage disequilibrium coefficients D' and r^2 between the six studied single-nucleotide polymorphisms

Single-nucleotide polymorphisms		rs4659200	rs3765945	rs2145418	rs7515409	rs4658973	rs1241
rs4659200	D'	—	0.35	0.02	0.09	0.12	0.12
	r^2		0.04	0.0004	0.0036	0.009	0.01
rs3765945	D'	0.35	—	0.04	0.01	0.09	0.04
	r^2	0.04		0.0004	0	0.006	0.001
rs2145418	D'	0.02	0.04	—	0.04	0.05	0.27
	r^2	0.0004	0.0004		0.0025	0.022	0
rs7515409	D'	0.09	0.01	0.04	—	0.47	0.11
	r^2	0.0036	0	0.0025		0.078	0.006
rs4658973	D'	0.12	0.09	0.05	0.47	—	0.12
	r^2	0.009	0.006	0.022	0.078		0.012
rs1241	D'	0.12	0.04	0.27	0.11	0.12	—
	r^2	0.01	0.001	0	0.006	0.012	

0.07 (95% CI, 0.03-0.18; $P < 0.0001$), respectively. The odds ratio of the T allele heterozygous carriers is 5.7 times higher than the odds ratio of the homozygous GG, indicating that the individuals with at least one risk allele (T variant) for this locus have increased risk for thyroid cancer. The rs2145418 and rs4658973 markers show weak association in the control population ($D' = 0.05$, $r^2 = 0.022$), suggesting that the effect in thyroid cancer susceptibility is not due to linkage disequilibrium between both markers. Thus, each of these single-nucleotide polymorphisms would be associated to different unknown susceptibility genes that are randomly transmitted. On the other hand, because the interaction between genotypes at different loci might influence phenotype outcomes, we analyzed the interaction of genotypes at the rs2145418 and rs4658973 loci. However, nonstatistically significant interaction was found ($P = 0.089$). In addition, because clinicopathologic characteristics might influence the risk for thyroid cancer of the different genotypes of the rs2145418 and rs4658973 polymorphisms in the patients group, we investigated this effect, but no differences with respect to sex, age of cancer diagnosis, and type of thyroid cancer were found.

Discussion

Studies on genetic susceptibility for thyroid cancer could have important relevance to understand the etiology of this pathology. Thus, association studies aimed to identify genes for thyroid cancer risk have been recently published (9-12), although no specific genes for thyroid cancer susceptibility have yet been described. Our previous study, using the BAT-40 marker in a case-control study, indicated that the chromosome 1p12-13 is related to thyroid cancer susceptibility (13). Therefore, in the present study, we aimed to map the susceptibility loci on this region. In this context, we have scanned a region of ~2.4 Mb surrounding the BAT-40 marker by genotyping six single-nucleotide polymorphisms in a Spanish population. This study has allowed us to identify in our population two independent genetic susceptibility loci on chromosome 1p12.

Association analysis using a case-control design showed a strong association between the rs2145418 marker and thyroid cancer incidence, and similar results were found with the rs4658973 marker. Thus, the variant allele for the rs2145418 marker and the overrepresented

Table 4. Genotype distribution and association analysis of six single-nucleotide polymorphisms at the 1p12-13 region

Single-nucleotide polymorphism	Genotype	Controls [n (%)]	Patients [n (%)]	Odds ratio* (95% CI)	P [†]
rs4659200	CC	54 (39.7)	85 (42.5)	1.0 (reference)	0.18
	TC	57 (41.9)	89 (44.5)	0.9 (0.62-1.60)	
	TT	25 (18.4)	26 (13.0)	0.7 (0.35-1.26)	
rs3765945	TT	55	74 (37.2)	1.0 (reference)	0.56
	CT	71 (52.2)	109 (54.8)	1.1 (0.72-1.81)	
	CC	10 (7.4)	16 (8.0)	1.2 (0.50-2.82)	
rs2145418	TT	87 (64.0)	44 (22.3)	1.0 (reference)	<0.0001
	TG	34 (25.0)	85 (43.1)	5.0 (2.80-8.83)	
	GG	15 (11.0)	68 (34.5)	9.2 (4.50-18.6)	
rs7515409	TT	54 (26.7)	65 (29.3)	1.0 (reference)	0.27
	CT	112 (55.4)	113 (50.9)	0.8 (0.54-1.31)	
	CC	33 (16.3)	44 (19.8)	1.1 (0.62-1.97)	
rs4658973	TT	60 (30.9)	127 (59.3)	1.0 (reference)	<0.0001
	GT	95 (48.9)	81 (37.9)	0.4 (0.26-0.62)	
	GG	39 (20.1)	6 (2.8)	0.07 (0.03-0.2)	
rs1241	TT	52 (38.5)	92 (45.8)	1.0 (reference)	0.08
	CT	75 (55.6)	92 (45.8)	0.7 (0.44-1.09)	
	CC	8 (5.9)	17 (8.4)	1.2 (0.49-1.16)	

*Crude odds ratio.
[†] P value corresponding to a codominant model.

allele for the rs4658973 marker in the patients group show an estimation of 5.0- and 5.7-fold increase of risk to thyroid cancer in heterozygous carries, respectively. This risk is double in homozygous carriers, which is in accordance with a codominant model. These polymorphisms are 377 kb distant, they show weak association, and no genotype interaction was found between them, indicating that their relation with thyroid cancer susceptibility is independent. At present, no risk factors for thyroid cancer or other type of cancer have been reported to map in this region, although alterations in the1p12-13 region have been described in different tumors (14-17).

The single-nucleotide polymorphisms analyzed in this study were selected as genetic markers for susceptibility loci. These single-nucleotide polymorphisms reside in noncoding sequences; therefore, we would not expect rs4658973 and rs2145418 to be the cause of their association with thyroid cancer. Nevertheless, the disease-associated rs4658973 marker maps into a region containing three overlapping genes (Fig. 1). The *WDR3* (member of the conserved family of WD-repeat genes), the *SPAG1* (sperm-associated antigen 17 gene), and the *GDAP2* (ganglioside-induced differentiation-associated protein 2 gene). Specifically, rs4658973 is located within the 24 introns of the *WDR3* gene, which overlaps the UTR 3′of the *SPAG17* gene. In addition, the *WDR3* and *GDAP2* genes run in opposite directions, and both promoter regions are overlapped. Thereby, any of these genes could be related to thyroid cancer susceptibility. In particular, WDR3, as a member of the WDR-repeat proteins, could be involved in several cellular processes, including cell cycle progression and signal transduction (20, 21). An irregular expression of some of the WDR-repeat proteins has been found in certain types of cancer (22-25). On the other hand, GDAP2 belongs to the GDAP1-10 protein family involved in signal transduction pathways (26). Then, we cannot rule out the possible effect of the *WDR3* and/or *GDAP2* genes in the risk for thyroid cancer, although more investigations are needed to define the thyroid cancer susceptibility causal gene in this region.

On the other hand, there are neither defined nor predicted genes in the rs2145418 region. The closer gene region to rs2145418 is the region containing the rs4658973 marker that we have previously mentioned, which is 377 kb upstream (see Fig. 1). The other end of rs2145418, 550 kb downstream, maps the *TBX15* gene involved in developmental processes (27, 28). Hence, nonevidences exist for hypothetical functional genes that could explain the strong association of the rs2145418 marker with thyroid cancer found in our study. Alternatively, the rs2145418 single-nucleotide polymorphism could reside in a regulatory sequence that might alter the expression of causal genes mapping near or a certain distance from this marker.

In conclusion and as we previously suggested, our results show a strong association between the chromosome 1p12 and thyroid cancer risk in a Spanish population. Our studies are the first describing susceptibility loci for thyroid cancer in this region and provide justification for further genetic analysis of the chromosome 1p12 region in other populations, as well as the investigation of the causal genes for thyroid cancer susceptibility in this region of chromosome 1.

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Cancer Epidemiol Biomarkers Prev 2008;17:1499-1504.

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