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Long non-coding RNA *ANRIL* polymorphisms in papillary thyroid cancer and its severity

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ABSTRACT

Background: Long non-coding RNAs are likely to have a role in the pathogenesis of many diseases, including cancer. We hypothesised an effect of certain *ANRIL* single nucleotide polymorphisms (SNPs) in papillary thyroid cancer.
Methods: Genomic *ANRIL* SNPs in rs11333048, rs4977574, rs1333040 and rs10757274 were determined in 134 papillary thyroid cancer patients and 155 age- and sex-matched controls.
Results: None of the ANRIL SNPs were individually linked to papillary thyroid cancer. However, the AAAC haplotype (A from rs11333048, A from rs4977574, A from rs1333040 and C from rs10757274, respectively) showed a protective effect from papillary thyroid cancer whilst the CAAC and CAGT haplotypes were associated with cancer. The rs1333048 CC variant was more frequent in patients with larger tumour size (≥1 cm) in a recessive model (OR 3.4 [95%CI, 1.1–11], P = 0.035). The rs4977574 AC variant was associated with smaller tumour size in an over-dominant model (OR 0.4 [95%CI, 0.2–1.0], P = 0.041). SNPs in rs10757274 (AA: p = 0.045) and rs1333040 (CC: p = 0.019) are linked to a lower likelihood of III–IV cancer stages in dominant or codominant models.
Conclusions: Certain haplotypes of *ANRIL* SNPs are associated with papillary thyroid cancer. ANRIL rs1333048 and rs4977574 variants were associated with larger and smaller tumour sizes, respectively. rs10757274 and rs1333040 variants might lead to lower III–IV cancer stages. These SNPs may be important in the diagnosis of this form of thyroid cancer.

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ANRIL; gene; papillary thyroid cancer; single nucleotide polymorphism; SNP

Introduction

Thyroid cancer is the most common endocrine malignancy whose worldwide incidence has sharply increased in recent years with more than 50,000 new cases diagnosed in 2018 [1]. Papillary thyroid cancer is the most common histological type, comprising 85% of cases [2], risk factors including radiation exposure (during childhood), nodular disease of the thyroid and a family history [3]. Several gene single nucleotide polymorphisms (SNPs) have been implicated in its carcinogenesis, tumour suppression, tumour growth, invasion, and metastasis [4–6].

Although ~75% of the human genome is transcribed into RNAs, <2% is ultimately translated into protein, indicating that ~98.5% of genomic DNA is composed of non-coding RNAs (ncRNAs), one form being long-non coding RNAs (lncRNAs) [7–9]. Numerous studies have showed that these molecules are involved in various biological and pathological processes, including development, proliferation, metastasis, fate decision, invasion and migration. These processes play critical roles in a wide range of the regulation of gene expression, chromatin remodelling, transcription, and posttranscriptional processing, whilst certain lncRNAs may act as tumour suppressors or oncogenes in the development of many human cancers [10–12].

Many lncRNAs, including MALAT1, HOTAIR and ANRIL, are associated with various disorders such as cancer [9]. ANRIL (CDKN2B antisense RNA 1) has a large gene with an estimated size of 126.3kb, located at 9p21, a region that encodes tumour suppressors, including p16INK4a, p14ARF and p15INK4b [13]. Dysregulated ANRIL is present in hepatocellular carcinoma, lung cancer and bladder cancer [14–16]. In the meta-analysis of Gao et al., abnormal expression of the majority of lncRNAs was significantly associated with the survival of gastric cancer patients [17]. Xiang et al. demonstrated that aberrant expression of many lncRNAs may be biomarkers of thyroid cancer [18], whilst Zhu et al. reported that the Onco-lncRNA HOTAIR rs920778T allele is linked to papillary thyroid cancer and an increase in HOTAIR RNA expression [19]. Other studies have investigated links between lncRNAs SNPs and papillary thyroid cancer [20,21]. We hypothesised links between *ANRIL* SNPs and papillary thyroid cancer and certain of its clinical features.

Materials and methods

We tested our hypothesis in a case-control study of 134 patients with papillary thyroid cancer and 155 sex- and age-matched controls with no history of any

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type of cancer or other diseases. All cases and controls were recruited from the Ali-ebn AbiTaleb Hospital, Zahedan, Iran, between January 2016 and February 2017. Papillary thyroid cancer was diagnosed according to fine needle aspiration cytology and was confirmed by two pathologists. Exclusion criteria were other thyroid diseases, thyroid surgery, neck irradiation or exposure to iodinated contrast media in the last 6 months, and other cancer [22]. The local Ethics Committee of Zahedan University of Medical Sciences approved the project (IR.ZAUMS.REc.1397.36), and written informed consent was obtained from all the participants.

The human genomic DNA was isolated from 500 µl K2 EDTA-treated peripheral blood using the salting out method and stored at −20 °C in nuclease-free distilled water. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to genotype four SNPs in *ANRIL* (rs11333048 A > C, rs4977574 A > G, rs10757274 A > G and rs1333040 C > T) as previously described [22]. The primer sequences, restriction enzymes and the amplicon sizes are displayed in Table 1. PCR amplification was performed in a final volume of 18 µL, which contained 9 *µ*l of 2X master mix, 1 µL each primer (10 µM), 6 µL deionized water and 1 µL template DNA (~100 ng/µL). The cycling program and primer sequences, restriction enzymes and the amplicon sizes have been described [23,24]. The digested fragments were separated by 2% agarose gel electrophoresis which stained with Sybr green.

Statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL, USA). Clinical and demographic characteristics of the both groups were evaluated using Student's t-test or Fisher's exact test. The associations between *ANRIL* genotypes and risk of PTC or its clinical features were estimated by computing the odds ratio (OR) and their 95% confidence intervals (95% CI) by logistic regression analyses. HaploView was used for analysis of the effect of each haplotype on PTC and Linkage Disequilibrium.

Results

The cases and controls were age (34.6 ± 11.9 vs 35.1 ± 11.6 years, respectively, P = 0.641) and sex (males 18.7% in cases and 19.3% in controls (P = 0.995)) matched. The clinical features of PTC group are presented in Table 2. There were no differences in genotypes of *ANRIL* rs1333048, rs4977574, rs10757274 and rs1333040 SNPs between cases and controls in codominant, dominant, recessive and over-dominant models (Table 3). Haplotype analysis indicated that AAAC haplotype was more frequent in control than PE women (24.3 vs 15.1 %) and associated with a decreased risk of PTC (P = 0.006). However, in combination, the CAAC (C from rs1333048, A from rs4977574, A from rs10757274 and C from rs1333040) and CAGT haplotypes were more frequent in papillary thyroid cancer than in controls at 7.6 vs 3.6% (p = 0.034) and 7.3 vs 3.2% (p = 0.025).

The possible association of tumour size and stage and rs1333048, rs4977574, rs10757274 and rs1333040 SNPs were sought in codominant, dominant, recessive and over-dominant models (Table 4). The frequency of rs1333048 CC genotype was higher than AA genotype

Table 2. Demographic and clinical characteristics of papillary thyroid cancer (PTC) patients.

Clinical characteristics	PTC n = 134
Location	
Right Lobe	59(44)
Left Lobe	61(45.5)
Both Lobes	14(10.5)
Tumour Size	
<1 cm	26(19.4)
≥1 cm	94(70.2)
Unknown	14(10.4)
TNM stage	
I	78(58.2)
II	15(11.2)
III	13(9.7)
IV	10(7.5)
Unknown	18(13.4)
N stage	
N0	79(59)
N1	36(26.9)
Unknown	19(14.1)
M stage	
M0	109(81.3)
M1	6(4.5)
Unknown	19(14.2)
Vascular invasion	
Positive	18(13.4)
Negative	99(73.9)
Unknown	17(12.7)
Capsular invasion	
Positive	19(14.2)
Negative	97(72.4)
Unknown	18(13.4)
Extrathyroidal expansion	
Positive	15(11.2)
Negative	99(73.9)
Unknown	20(14.9)

Table 1. The PCR-RFLP information of *ANRIL* polymorphisms.

Polymorphism	Chr: position	Restriction enzyme	Fragment length (bp)	PCR primers (5′→3′)	Annealing (*c*)
rs1333048	22125348	Dra I	AA: 84 and 68 pb CC: 152 bp	F:ACCCGAAGTAGAGCTGCAAA R:CACAAGTTGGAATATGAAGCAGA	51
rs4977574	22098575	Hin6I	AA: 308 pb GG: 270 bp	F: GGTAGCCCACCACTCCCCTAAAG R: ATCAGCTGCCTGTCCTTGGACTA	50
rs10757274	22096056	BsmAI	AA:172 and 78bp GG: 250 bp	F:GTTTCTGCACATGGTGATGG R:CTGCCTCACTCTCCAGTTCC	59
rs1333040	22083405	BsmI	CC: 220 and 166 pb TT: 386bp	F:CATACAGAGATGAACTAACTTGCTC R:GAGATTCTGATTCAGAATATTCAAG	52

Table 3. Allelic and genotypic frequency of *ANRIL* polymorphisms in 134 papillary thyroid cancer patients and 155 controls.

	N(%)			Co-dominant OR (95%CI) p value		Dominant OR (95%CI) p value	Recessive OR (95%CI) p value	Over-dominant OR (95%CI) p value
rs1333048 A/C	***AA***	***AC***	***CC***	***AC vs AA***	***CC vs AA***	***AC+CC vs AA***	***CC vs AC + AA***	***AC vs AA+ CC***
Controls	29(18.7)	77(49.7)	49(31.6)					
Cases	17(12.7)	69(51.5)	48(35.8)	1.53(0.77–3.02) 0.222	1.67(0.81–3.42) 0.162	1.58(0.83–3.03) 0.165	1.21(0.74–1.97) 0.450	1.08(0.68–1.71) 0.758
rs4977574 A/G	***AA***	***AG***	***GG***	***AG vs AA***	***GG vs AA***	***AG +GG vs AA***	***GG vs AG+ AA***	***AG vs AA+ GG***
Controls	42(27.1)	70(45.2)	43(27.7)					
Cases	46(34.3)	58(43.3)	30(22.4)	0.76(0.44–1.30) 0.315	0.64(0.34–1.19) 0.158	0.69(0.42–1.14) 0.144	0.75(0.44–1.29) 0.297	0.90(0.56–1.43) 0.654
rs10757274 A/G	***AA***	***AG***	***GG***	***AG vs AA***	***GG vs AA***	***AG +GG vs AA***	***GG vs AG+ AA***	***AG vs AA+ GG***
Controls	37(23.9)	77(49.7)	41(26.5)					
Cases	36(26.9)	56(41.8)	42(31.3)	0.75(0.42–1.33) 0.320	1.05(0.56–1.98) 0.873	0.85(0.50–1.45) 0.559	1.27(0.76–2.12) 0.360	0.75(0.47–1.19) 0.225
rs1333040 C/T	***CC***	***CT***	***TT***	***CT vs CC***	***TT vs CC***	***CT+ TT vs CC***	***TT vs CT + CC***	***CT vs CC + TT***
Controls	28(18.1)	61(39.4)	66(42.6)					
Cases	23(17.2)	55(41)	56(41.8)	1.09(0.57–2.13) 0.782	1.03(0.54–1.99) 0.923	1.06(0.58–1.95) 0.841	0.97(0.61–1.55) 0.892	1.11(0.69–1.77) 0.674

OR = odds ratio; CI = confidence interval.

Table 4. Association of *ANRIL polymorphisms* with clinical characteristics of papillary thyroid carcinoma.

				OR (95% CI) p value				
Characteristics				Codominant		Dominant	Recessive	Over-dominant
rs1333048 A/C	*AA*	*AC*	*CC*	*AC vs AA*	*CC vs AA*	*AC+CC vs AA*	*CC vs AC + AA*	*AC vs AA+ CC*
Tumour size, cm								
<1	6(23.1)	16(61.5)	4(15.4)					
≥1	11(11.7)	47(50.0)	36(38.3)	1.60 (0.51–5.04) 0.420	4.91 (1.17–20.60) 0.030	2.26 (0.75–6.86) 0.148	3.41 (1.09–10.71) 0.035	0.63 (0.26–1.52) 0.299
rs4977574 A/G	*AA*	*AG*	*GG*	*AG vs AA*	*GG vs AA*	*AG +GG vs AA*	*GG vs AG+ AA*	*AG vs AA+ GG*
Tumour size, cm								
<1	6(23.1)	15(57.7)	5(19.2)					
≥1	38(40.4)	34(36.2)	22(23.4)	0.36 (0.13–1.03) 0.056	0.70 (0.19–2.54) 0.582	0.42 (0.16–1.15) 0.092	1.28 (0.43–3.80) 0.653	0.40 (0.16–0.96) 0.041
rs10757274 A/G	*AA*	*AG*	*GG*	*AG vs AA*	*GG vs AA*	*AG +GG vs AA*	*GG vs AG+ AA*	*AG vs AA+ GG*
TNM stage								
I–II	22(23.7)	40(43)	31(33.3)					
III–IV	10(45.4)	6(27.3)	6(27.3)	0.33 (0.11–1.03) 0.056	0.43 (0.14–1.35) 0.146	0.37 (0.14–0.98) 0.045	0.75 (0.27–2.11) 0.585	0.48 (0.17–1.32) 0.155
rs1333040C/T	*CC*	*CT*	*TT*	*CT vs CC*	*TT vs CC*	*CT+ TT vs CC*	*TT vs CT + CC*	*CT vs CC + TT*
TNM stage								
I–II	13 [14]	40(43)	40(43)					
III–IV	8(36.4)	8(36.4)	6(27.3)	0.33 (0.10–1.04) 0.058	0.24 (0.07–0.83) 0.024	0.28 (0.10–0.81) 0.019	0.50 (0.18–1.38) 0.181	0.73 (0.28–1.89) 0.511

in patients with a larger tumour size (≥1 cm). In addition, this SNP was associated with larger tumour size in a recessive model. The rs4977574 AG genotype was more frequent in patients with smaller tumour size (<1 cm) and this SNP may protect patients from a larger tumour size in an over-dominant model. The frequency of rs10757274 AG was associated with a lower risk of higher cancer stages (III–IV) in a dominant model. Moreover, the rs1333040 SNP was associated with a lower risk of stages III–IV in codominant (TT vs CC) and dominant (CT+TT v CC) models.

Discussion

We tested the hypothesis that there are differences in certain *ANRIL* rs1333048, rs4977574, rs10757274 and rs1333040 SNPs in papillary thyroid cancer. Although we found no relationship between individual variants and the disease, there were differences when SNPs were combined. Our data suggest that the AAAC haplotype could be a protective factor, and the CAAC and CAGT haplotypes could be risk factors for papillary thyroid cancer. *ANRIL* rs1333048 SNP was associated with a larger tumour size in a recessive model whilst rs4977574 SNP was associated with smaller tumour size in an over-dominant model. Finally, rs10757274 and rs1333040 SNPs may be related to III–IV cancer stages in dominant or codominant models.

LncRNAs are involved in regulating and controlling various biological processes, such as in the regulatory mechanisms of gene expression in transcriptional or post-transcriptional stages [8,11]. Some, such as CCAT2 and HOTTIP, may be act as oncogenes [25,26], while others, including GAS5 and ANRIL, play a tumour-suppressor role [12,27]. Several studies have suggested that aberrant expression of lncRNAs is involved in different malignancies, including gastric, colorectal, and papillary thyroid carcinoma [28–30]. Various papillary thyroid cancer-related lncRNAs, and their

clinical significance and function have been identified. Huang et al. showed that overexpression of CASC2 leads to suppressed cell proliferation and promoted apoptosis in papillary thyroid cancer [30], whilst Chen et al. reported that CNALPTC1 is upregulated in papillary thyroid cancer and is associated with aggressive clinical characteristics [31]. A meta-analysis by Xiang et al. demonstrated that aberrant expression of many lncRNAs may be biomarkers for thyroid cancer [18].

Zhao et al. described significant roles of ANRIL in the development of invasion and metastasis of thyroid cancer cells by reduced expression of tumour suppressor gene p15INK4b through inhibiting transforming growth factor (TGF)-β/Smad signalling pathway [32]. In addition, Liu et al. showed that ANRIL was up-regulated, associated with poor prognosis and promoted tumorigenesis of oral squamous cell carcinoma [33] whilst Cheng et al. showed that knockdown of ANRIL expression significantly reduced the proliferation, migration and invasion of osteosarcoma cells in vitro and demonstrated that it might play a role in the cellular biology and oncogenesis of osteosarcoma cells [34]. Similarly, Huang et al. reported that the expression of ANRIL is increased in hepatocellular carcinoma [14]. ANRIL has been identified as an oncogene in a number of malignancies, such as bladder cancer, hepatocellular carcinoma, and oesophageal squamous cell carcinoma [14,16,35]. Heidari et al. showed that let7a-2 rs1143770 CT and TT SNPs are linked to papillary thyroid cancer [36].

The findings of a meta-analysis by Huang et al. showed that three polymorphisms (rs1333048, rs4977574, and rs10757278) of *ANRIL* but not rs1333045 were linked with cancer [37], whilst Taheri et al. showed similar findings with prostate cancer [38] and Timofeeva et al. demonstrated that rs1333040 is associated with squamous cell carcinoma [39]. Although there are few studies which investigate the association between *ANRIL* genetic variants and the risk of cancer, several studies have examined association between these variants and the risk of atherosclerosis [40].

We recognise some limitations to our data. For example, the relatively small sample size in analysis of genotypes with respect to histological features and lack of an ANRIL expression assay. Further studies are still needed to evaluate these findings. Indeed, similar studies with different ethnic groups are necessary to confirm or refute our results. Our data represent an advance in biomedical science because it points to roles for combinations of ANRIL rs1333048, rs4977574, rs10757274 and rs1333040 SNPs in the diagnosis and staging of papillary thyroid cancer.

Summary table

What is known about this subject?

- Altered expression of certain lncRNAs is present in a numberof cancers.
- LncRNA ANRIL expression is altered in bladder, lung andhepatocellular carcinoma.

What this work adds

- Individually, *ANRIL* variants rs11333048, rs4977574, rs1333040 and rs10757274 are not linked to papillary thyroid cancer.
- Haplotype combinations of these variants can diagnose papillary thyroid cancer.
- *ANRIL* variants are linked to tumour size or the stage of the papillary thyroid cancer.

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Disclosure statement

The authors declare that they have no conflict of interest.

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