# Association of the Oncostatin M Receptor Gene Polymorphisms with Papillary Thyroid Cancer in the Korean Population

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***Objectives.*** To investigate the association between papillary thyroid cancer (PTC) and single nucleotide polymorphisms (SNPs) of oncostatin M receptor (*OSMR*) in the Korean population.

***Methods.*** Retrospective case-control study was done. Eighty-five patients with PTC and 287 controls were studied. One missense SNP (rs2278329, Asp553Asn) and one promoter SNP (rs2292016, -100 G/T) of the *OSMR* gene were genotyped by direct sequencing. Genetic data were analyzed using the SNPStats, Helixtree, and SNPAnalyzer Pro. PTC patients were dichotomized and compared with respect to the clinicopathologic characteristics.

***Results.*** There was no association between genotypes and allele frequencies of OSMR SNPs (rs2278329 and rs2292016) and PTC susceptibility. SNP rs2278329 was significantly associated with tumor size (dominant model; $P=0.028$; odds ratio [OR], 2.71; 95% confidence interval [CI], 1.12 to 6.57). The A allele was higher in sizes large than 1 cm (32.5% vs. 16.7%; $P=0.018$; OR, 2.41; 95% CI, 1.17 to 4.98). Regarding the number of tumors, we found no significant association with genotype, however, the A allele was higher in patients with multifocaltiy (33.3% vs. 19.1%; $P=0.040$; OR, 2.12; 95% CI, 1.03 to 4.34).

***Conclusion.*** The results suggest that *OSMR* polymorphism rs2278329 is associated with clinicopathologic characteristics of the tumor growth and multifocality development.

***Key Words.*** *Papillary thyroid cancer, Oncostatin M receptor, Single nucleotide polymorphism, Clinicopathologic status*

## INTRODUCTION

Papillary thyroid cancer (PTC) is the most common type of dif-

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ferentiated thyroid carcinoma which accounts for at least 70% of all follicular-cell derived thyroid cancer, and its incidence has been increasing (1). Although the prognosis of PTC is generally good, up to 10% of patients would eventually die of the disease or face the morbidity of recurrence (2). Tumor staging, which is predictive of prognosis, is based on the size and extent of the primary tumor and the presence of lymph node or distant metastasis (2).

The oncostatin M receptor (*OSMR*) gene, located 5p13.1, encodes a protein called OSMRβ which heterodimerizes with interleukin (IL) 6 signal transducer (gp130) to form type II OSMR (3, 4). Once recruited, the receptor complexes allow the activation of Janus protein tyrosine kinase (JAK) and, subsequently, the activation of signal transducer and activator of transcription (STAT, mainly STAT3) and mitogen activated protein kinase (MAPK) (5-7). In melanoma or other solid tumors, the key role

of STAT3 is to mediate the growth inhibitory effect of OSM (8).

The OSM is a member of the IL6 family which is now considered a multifunctional cytokine that is implicated in the activation, proliferation and/or differentiation of several cell types, such as hepatocytes, osteoblasts and lung epithelial cells (7, 9, 10). OSM is more active than IL6 in inhibiting the proliferation of numerous solid tumor cell lines derived from breast or lung cancer, hepatoma, osteosarcoma and melanoma (9). In addition, it was reported to stimulate AIDS-related Kaposi's sarcoma, myeloma, plasmacytoma, and human prostate cancer (11-14). OSM is a potent inhibitor of iodine metabolism and was show to decrease thyroid peroxidase mRNA levels in porcine thyroid cells (4). Iodide oxidation and coupling activities of thyroid peroxidase are significantly lower in PTC than in diffuse goiter and benign adenoma (15).

Although OSM and its interaction with OSMR are related to PTC development and clinical characteristics, no genetic studies of this interaction between OSMR and PTC have been conducted. Thus, in the present study, we investigated whether single nucleotide polymorphisms (SNPs) of *OSMR* contribute to the development of PTC. Also, we assessed the association of SNPs of *OSMR* with clinicopathologic characteristics of PTC in the Korean population.

## MATERIALS AND METHODS

### Subjects
Patients with PTC were recruited from the Kyung Hee University Hospital, Seoul, Korea. The PTC group included 85 patients (23 males and 62 females; mean of age, 53.2 years). A diagnosis of PTC and the presence of cervical regional lymph node metastasis were both confirmed by pathologic examination. A total of 287 normal controls (156 males and 131 females; mean of age, 37.6 years) were included for comparison. None of the controls were found to have any malignancy or thyroid disease at enrollment. Written informed consent was obtained from all individuals according to the Declaration of Helsinki guidelines. This study was approved by the Institutional Review Boards of the Medical Research Institute, Kyung Hee University Medical Center.

### Patients' profile and clinical data
To determine the association between the SNPs of OSMR and the clinicopathologic characteristics of PTC, patients were divided into subgroups according to size (≤1 cm vs. >1 cm), number (unifocality vs. multifocaltiy), bilaterality (unilateral vs. bilateral) of tumors, presence or absence of extrathyroidal invasion, lymph node metastasis and angiolymphatic invasion. The demographic characteristics of PTC patients and controls are shown in Table 1.

**Table 1.** Clinicopathologic characteristics of the study population with papillary thyroid carcinoma

| Characteristics | Values |
| --- | --- |
| Age (years) | 53.2±11.5 |
| Sex (male/female) | 23/62 |
| Tumor size >1 cm | 40 (47) |
| Multifocal | 30 (35) |
| Bilateral | 26 (31) |
| Extrathyroidal invasion | 43 (51) |
| Cervical lymph node metastasis | 24 (28) |
| Angiolymphatic invasion | 5 (6) |

Values are presented as mean±SD or number (%).

### SNP selection and genotyping
The SNPs of the *OSMR* gene were selected using the database found at http://ncbi.nlm.nih.gov/SNP, dbSNP BUILD 131. Of the SNPs in the *OSMR* coding region, SNPs with low heterozygosity (below 0.1; rs16867807, rs35207712, rs35117676, rs35727755, rs34324145, rs35546805, rs2289925, rs2289926, rs35739767, rs3749737, and rs34080825), without Asian population (rs34675408), and without genotype information (rs10941412) were excluded. In the promoter region, SNPs with low heterozygosity (below 0.1; rs76020575), a low minor allele frequency (below 0.05; rs540558), a mono genotype (rs5867434), and without genotype information (rs79913282, rs3763098, and rs13359039), were excluded. Finally, we selected the SNPs rs2278329 (missense, Asp553Asn) and rs2292016 (promoter, -100 G/T) and their heterozygosities were 0.226 and 0.242, respectively. Blood samples for DNA extraction from each subject were collected in EDTA tube and then stored in a -80°C refrigerator. Genomic DNA was extracted using a QIAamp DNA mini kit (QIAGEN, Valencia, CA, USA). SNP genotyping was determined by direct sequencing. Genomic DNA was amplified using the following primers: rs2278329 (sense, 5′- CCACCCAA GCACCTGTAACTAT-3′; antisense, 5′- CTAACACCCATGCTG-GATTTGT-3′; 461 bp), rs2292016 (sense, 5′-GGACTTCTCTT-GCCTGAAGATT-3′; antisense, 5′- AGGAATTCCCTCCCTTCA GTC-3′; 347 bp). Polymerase chain reaction products were sequenced using an ABI Prism 3730XL analyzer (PE Applied Biosystems, Carlsbad, CA, USA). Sequence data were analyzed using SeqManII software (DNASTAR Inc., Madison, WI, USA).

### Statistics
For all SNPs, Hardy-Weinberg equilibrium was assessed using SPNStats software (http://bioinfo.iconcologia.net/index.php? module=Snpstats). Helixtree (Golden Helix Inc., Bozeman, MT, USA) and SNPAnalyzer Pro (ISTECH Inc., Goyang, Korea) were used to analyze the genetic data. Multiple logistic regression models (codominant, dominant, and recessive) were performed, after adjustment for sex and age, for odds ratios (ORs), 95% confidence intervals (CIs), and corresponding *P*-values. Linkage disequilibrium (LD) block of polymorphisms was tested using

Table 2. Genotype and allele frequencies of oncostatin M receptor (OSMR) polymorphisms in patients with papillary thyroid cancer and in controls

|  |  |  | PTC | Control | Model | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|
| rs2278329 | Genotypes | G/G | 49 (57.6) | 138 (48.2) | Codominant1 | 1.64 (0.59–4.58) | 0.342 |
| missense |  | A/G | 31 (36.5) | 117 (40.9) | Codominant2 | 2.20 (0.81–5.98) | 0.122 |
| (Asp553Asn) |  | A/A | 5 (5.9) | 31 (10.8) | Dominant | 1.95 (0.73-5.17) | 0.182 |
|  |  |  |  |  | Recessive | 1.46 (0.90–2.38) | 0.129 |
|  | Alleles | G | 129 (75.9) | 393 (68.7) |  | 1.43 (0.97-2.12) | 0.073 |
|  |  | A | 41 (24.1) | 179 (31.3) |  | 1 |  |
| rs2292016 | Genotypes | G/G | 48 (57.1) | 126 (46.1) | Codominant1 | 0.97 (0.41–2.34) | 0.953 |
| promoter |  | T/G | 28 (33.3) | 115 (42.1) | Codominant2 | 1.52 (0.66–3.54) | 0.327 |
| (-100 G/T) |  | T/T | 8 (9.5) | 32 (11.7) | Dominant | 1.26 (0.56–2.85) | 0.577 |
|  |  |  |  |  | Recessive | 1.56 (0.95–2.55) | 0.079 |
|  | Alleles | G | 124 (73.8) | 367 (67.2) |  | 1.38 (0.93 – 2.03) | 0.108 |
|  |  | T | 44 (26.2) | 179 (32.8) |  | 1 |  |

*P*-values were from logistic regression analyses with the codominant1 (A/A vs. A/G), codominant2 (A/A vs. G/G), dominant, and recessive models controlling age and gender as covariates. Values are presented as number (%).
PTC: papillary thyroid cancer; OR: odds ratio; CI: confidence interval.

Haploview version 4.2 (http://www.broadinstitute.org/haploview/haploview). The online program AliBaba 2.1 (http://www.gene-regulation.com/pub/programs/alibaba2) was used to determine whether SNPs affect transcription factors. The data were analyzed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). For all statistical tests, the significance level was set at *P*<0.05.

## RESULTS

### Genotypic and allelic frequency of rs2278329 and rs2292016
The genotypic and allelic frequencies of rs2278329 and rs2292016 in PTC patients and controls are given in Table 2. The observed genotype distributions of the SNPs were in Hardy-Weinberg equilibrium (*P*>0.05, data not shown).

No association between the genotype and allele frequencies of rs2278329 and rs2292016 were observed in the 85 PTC patients and 287 control subjects (Table 2). In the measurement of LD, no LD block was identified by the Gabriel method (16).

### Association between rs2278329 and rs2292016 and clinicopathologic characteristics
We analyzed the association of the *OSMR* gene polymorphisms with the clinicopathologic status of size (larger or smaller than 1 cm), number (unifocality or multifocality), and bilaterality (unilateral or bilateral) of tumors, and the presence or absence of lymph node metastasis, extrathyroidal invasion and lymphovascular invasion. For rs2278329, we found a significant association between PTC and tumor size (dominant model, G/G vs. A/G and A/A; *P*=0.028; OR, 2.71; 95% CI, 1.12 to 6.57) (Table 3). The frequencies of the G/G, A/G, and A/A genotypes were 68.9%, 28.9%, and 2.2% in sizes smaller than 1 cm, respectively, and 45%, 45%, and 10% in sizes larger than 1 cm, respectively. Additionally, there was a significant difference in the allele

frequency: the A allele was higher in sizes large than 1 cm (32.5% vs. 16.7%; *P*=0.018; OR, 2.41; 95% CI, 1.17 to 4.98). Regarding the number of tumors, we found no significant association with genotypes: however, there was a significant difference in allele frequency: the A allele was higher in patients with the multifocaltiy (33.3% vs. 19.1%; *P*=0.040; OR, 2.12; 95% CI, 1.03 to 4.34) (Table 3). However, we found no significant association with PTC in terms of bilaterality of tumors and presence of lymph node metastasis, extrathyroidal invasion and lymphovascular invasion.

We calculated the sample power to verify our data (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). In this study, the sample powers of each SNPs were 0.837 (rs2278329; number of cases for 80% power, 77) and 0.837 (rs2292016; number of cases for 80% power, 77), respectively. Accordingly, our results were acceptable.

We attempted to determine whether the promoter SNP rs2292016 affects transcription factors using the online program AliBaba 2.1. The T-containing sequences can bind with ICSBF transcription factor, but IRF-I substitutes for ICSBF in G-containing sequences. Assuming the change of transcript factor binds according to variants of SNP, this promoter SNP may affect the protein expression of OSMR.

## DISCUSSION

We found no association between the SNPs rs2278329 (missense, Asp553Asn) and rs2292016 (promoter, -100 G/T) of the *OSMR* gene and PTC susceptibility. However, we found an association between rs2278329 and clinicopathologic characteristics, such as the size and number of tumors.

OSMR is a specific receptor OSM which is a member of the IL6 family (4). OSM, produced mainly by activated monocytes

Table 3. Subgroup analysis according to the clinicopathologic status of the SNP rs2278329 Asp553Asn in papillary thyroid cancer after adjustment for sex and age

| Genotype | Size of tumors | | Model | OR (95% CI) | P-value |
|---|---|---|---|---|---|
| | >1 cm (n=40) | ≤1 cm (n=45) | | | |
| | Genotypes | | | | |
| G/G | 18 (45.0) | 31 (68.9) | Codominant1 | 2.39 (0.95–5.98) | 0.064 |
| A/G | 18 (45.0) | 13 (28.9) | Codominant2 | 6.89 (0.71–66.48) | 0.095 |
| A/A | 4 (10.0) | 1 (2.2) | Dominant | **2.71 (1.12–6.57)** | **0.028** |
| | | | Recessive | NA | 0.183 |
| | Alleles | | | | |
| G | 54 (67.5) | 75 (83.3) | | 1 | |
| A | 26 (32.5) | 15 (16.7) | | **2.41 (1.17-4.98)** | **0.018** |
| | Number of tumors | | Model | OR (95% CI) | P-value |
| | Multiple (n=30) | Single (n=55) | | | |
| | Genotypes | | | | |
| G/G | 13 (43.3) | 36 (65.5) | Codominant1 | 2.28 (0.88-5.90) | 0.089 |
| A/G | 14 (46.7) | 17 (30.9) | Codominant2 | 4.15 (0.62–27.72) | 0.141 |
| A/A | 3 (10) | 2 (3.6) | Dominant | 2.48 (1.00–6.16) | 0.051 |
| | | | Recessive | 2.94 (0.46-18.69) | 0.252 |
| | Alleles | | | | |
| G | 40 (66.7) | 89 (80.9) | | 1 | |
| A | 20 (33.3) | 21 (19.1) | | **2.12 (1.03-4.34)** | **0.040** |
| | Bilaterality of tumors | | Model | OR (95% CI) | P-value |
| | Bilateral (n=26) | Unilateral (n=59) | | | |
| | Genotypes | | | | |
| G/G | 12 (46.1) | 37 (62.7) | Codominant1 | 1.95 (0.74–5.15) | 0.179 |
| A/G | 12 (46.1) | 19 (32.2) | Codominant2 | 1.95 (0.74-5.15) | 0.458 |
| A/A | 2 (7.7) | 3 (5.1) | Dominant | 1.96 (0.77-5.00) | 0.157 |
| | | | Recessive | 1.56 (0.24-9.91) | 0.640 |
| | Alleles | | | | |
| G | 36 (69.2) | 93 (78.8) | | 1 | |
| A | 16 (30.8) | 25 (21.2) | | 1.65 (0.79-3.45) | 0.181 |

*P*-values were from logistic regression analyses with the codominant1 (G/G vs. A/G), codominant2 (G/G vs. A/A), dominant, and recessive models controlling age and gender as covariates. Values are presented as number (%).
OR: odds ratio; CI: confidence interval.

and lymphocytes, is well recognized as a cytostatic cytokine for some types of tumor cell derived from melanoma (17), breast cancer (18), colorectal cancer (19), and glioma cells (20). In contrast, OSM stimulates the growth of AIDS-related Kaposi's sarcoma (12), myeloma (13), and plasmacytoma (14). It promotes the growth of DU145 human prostate cancer cells through the signaling of the OSM specific receptor (11).

IL6 was shown to be related to aggressive behavior in thyroid cancer (21). Thyroid tumor cells originating from undifferentiated carcinomas express cytokines such as IL6, leukemia inhibitory factor, thyroid transcription factor-1, and paired box gene 8 (22). OSM is a potent inhibitor of iodine metabolism in thyroid cells and is thought to be one of the principal cytokines that counter thyroid dysfunction under severe illness such as sepsis (4). In this study, we found the association between the tumor size and SNP rs2278329 of the *OSMR* gene. Tumor size is related to the prognosis of PTC. Many studies have concluded that

PTC ≤ 1 cm diameter has an excellent prognosis and very low mortality rate, even though debate has centered on the clinical significance of PTC ≤ 1 cm (23-26). We also found the association between the multifocality and SNP rs2278329 of the *OSMR* gene. The relevance and importance of multifocality on prognosis are still obscure. According to Antonaci et al. (27), multifocal PTC showed aggressive biological biological and clinical features. In contrast, multifocality was not considered a prognostic determinant for the categorization of tumors as low risk or high risk in the study of Hay et al. (28). Although the relevance of the multifocality is debated, it is associated with indications for completion of thyroidectomy after lobectomy and for postoperative radioactive iodine ablation.

A missense mutation was identified in the *OSMR* gene in three families of familial primary localized cutaneous amyloidosis (FPLCA) (3). FPLCA is an autosomal dominant disorder associated with chronic skin itching and deposition of epidermal kera-

tin filament-associated amyloid material in the dermis (3). FPL-CA keratinocytes showed reduced activation of the JAD/STAT, MAPK, and p13K/Akt pathways after stimulation with OSM or the cytokine IL31 stimulation. The 2 pathogenic amino acid substitutions, 2072T-C transition (Ile691Thr substitution) and 1853G-C transversion (Gly618Ala) were located within the extracellular fibronectin type III like domains regions critical to receptor dimerization and function.

The human SNP database (dbSNP BUILD131) presents frequencies of genotype for rs2278329 (G/G:G/A:A/A; Chinese, 0.533:0.333:0.133; Japanese, 0.600:0.378:0.022; Korean in this study, 0.482:0.409:0.108) and rs2292016 (G/G:G/T:T/T; Chinese, 0.359:0.513:0.128; Japanese, 0.535:0.395:0.070; Korean in this study, 0.461:0.421:0.117). The allele frequencies of rs2278329 in the Korean population in this study (G, 0.687; A, 0.313) were similar to those observed in Chinese (G, 0.700; A, 0.300) and Japanese (G, 0.789; A, 0.211) populations. The allele frequencies of rs2292016 in the Korean population in this study (G, 0.672; T, 0.328) were also similar to those observed in Chinese (G, 0.615; T, 0.385) and Japanese (G, 0.733; T, 0.267) populations.

Our study has some limitations. First, sex ratio and mean age of controls differ in comparison with cases. However, the results from the large number of controls may overcome this problem. Second, the small number of patients may affect the statistical results, though the statistic power for analysis was reliable, so that a further study with large number of patients should be performed.

In conclusion, the *OSMR* polymorphism is associated with clinicopathologic characteristics of tumor growth and multifocaltiy development.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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