A missense polymorphism (rs11895564, Ala380Thr) of integrin alpha 6 is associated with the development and progression of papillary thyroid carcinoma in Korean population

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Purpose: Integrins play crucial roles in the pathogenesis of papillary thyroid carcinoma (PTC). The aim of this study was to investigate whether two single nucleotide polymorphisms (SNPs) (rs2141698, -1687A/G; rs11895564, Ala380Thr) of the integrin alpha 6 (ITGA6) gene are associated with the development and clinicopathologic characteristics of PTC such as the size (< 1 cm and ≥ 1 cm), number (unifocality and multifocality), location (one lobe and both lobes), extrathyroid invasion, and cervical lymph node metastasis. Methods: We enrolled 104 PTC patients and 318 control subjects. Genotypes of each SNP were determined by direct sequencing. SNPStats, SNPAnalyzer, and Helixtree programs were used to evaluate odds ratios (ORs), 95% confidence intervals (CIs), and P-values. Multiple logistic regression models were performed to analyze genetic data. Results: A missense SNP rs11895564 was associated with the development of PTC. The A allele frequency of rs11895564 was higher in PTC patients than in controls (13.5% vs. 7.1%; P = 0.005; OR, 2.04; 95% CI, 1.24 to 3.37). In the clinicopathologic characteristics, the A allele frequency of rs11895564 showed difference in the size (19.6% in < 1 cm vs. 6.9% in ≥ 1 cm; P = 0.010; OR, 0.30; 95% CI, 0.12 to 0.75) and number (8.5% in unifocality vs. 20.8% in multifocality; P = 0.015; OR, 2.85; 95% CI, 1.23 to 6.59) of PTC. Conclusion: These results suggest that the A allele of rs11895564 (Ala380Thr) in ITGA6 may be a risk factor of PTC, and also contribute to the progression of PTC in the Korean population.

Key Words: Integrins, alpha 6 (ITGA6), Papillary thyroid cancer, Polymorphism, Progression

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the predominant type of thyroid cancers and develops in the follicular cells of the thyroid. It is the most rapidly increasing cancer, probably because of the increased detection of small, low-risk PTC. The incidence of PTC rapidly increases worldwide during the past 10 to 20 years. According to the data from the National Cancer Center in Korea (http://www.cancer.go.kr), among adolescents and adults be-
tween ages 15 years and 64 years, thyroid cancer is the first most common cancer, and PTCs are the most common of all thyroid cancers. Most PTC patients with thyroidectomy following the treatments of thyroid hormone suppression and radioactive iodine ablation have a good prognosis. However, PTC recurs in some patients and is the major one of endocrine cancer deaths [1,2]. To date, the tailored target therapies for the patients who fail to respond to the initial treatment paradigm and who have the progressive and refractory cancers are being investigated. Environmental factors such as radiation, hormones, diet, and smoking are risk factors of PTC, and genetic factor has also implicated as a risk factor for the development and progression of PTC [3-5].

The extracellular matrix (ECM) (i.e., thrombospondin 1 [THBS1, also known as TSP1] and fibronectin 1 [FN1]) plays a crucial role in the maintenance of cell and morphogenesis of tissue. ECM interacts with the cell adhesion molecules (CAMs) including integrins, CD36, CD44, and the immunoglobulin superfamily. CAMs provide a force of physical link between ECM and the cytoskeleton [6-9]. The ECM-CAM interactions also affect in the tumor microenvironments such as tumor cell adhesion, proliferation, migration, invasion, and metastasis [10-12]. Integrins are transmembrane proteins and compose of an alpha chain and a beta chain. Integrin, alpha 6 (ITGA6) is a member of ECM adhesion receptor, and interacts beta chains, making the heterodimeric complexes consisting of one alpha chain and one beta chain (α6β1 and α6β4) [9,13]. Both α6β1 and α6β4 may play critical roles in the progression of cancers and be involved in the initial formation of cancerous tumors. Abnormal expression of α6β4 in the suprabasal cell layers has been associated with an increased malignancy of squamous cell carcinomas [10-12]. Integrins participate in cellular signalings such as the mitogen-activated protein kinase (MAPK)/nuclear factor of kappa light polypeptide gene enhancer in B-cells (NFκB), phosphoinositide-3-kinase (PI3) kinase/v-akt murine thymoma viral oncogene homolog (AKT), and mothers against decapentaplegic homolog (SMAD) signalings [14-16]. In particular, α6β1 directly bind THBS1 in thyroid cancer cells and this complex then activates the MAPK signaling. These actions may remodel the ECM microenvironments and elicit tumor cell invasion into the lymph node and other tissues from the basement membrane, causing the progression of thyroid cancer [17]. Although integrins may be involved in PTC susceptibility, the genetic determinants have not yet been fully defined.

In this study, we explored the relationship between ITGA6 SNPs and PTC, and their clinicopathologic characteristics in Korean population.

**METHODS**

We enrolled 104 PTC patients (29 males and 75 females) and 318 control subjects (105 males and 213 females). PTC patients were selected among participants who visit at the Departments of Surgery and Otolaryngology-Head and Neck Surgery. Subjects with nodular hyperplasia, anaplastic carcinoma, follicular carcinoma, double primary of PTC and follicular carcinoma, and follicular variant of PTC were excluded. PTC was confirmed by pathologic examinations. Controls were recruited from healthy participants through a general health check-up program. Subjects with thyroid disease, cancers, and any severe diseases were excluded. Informed consent was obtained from all subjects. This study was conducted in accordance with the guidelines of the Helsinki Declaration. Patients were divided into subgroups in accordance to the size (<1 cm and ≥1 cm), number (unifocality and multifocality), location (one lobe and both lobes), extrathyroidal invasion (present and absent), lymph node metastasis (present and absent), and angiolymphatic invasion (present and absent).

For the selection of ITGA6 SNPs, we searched the promoter and coding regions of the ITGA6 gene in the SNP database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP, BUILD 132). The SNPs with unknown heterozygosity or heterozygosity below 0.1 and unknown minor allele frequency (MAF) or MAF below 0.1 were excluded. Out of 14 promoter SNPs, there were 3 unknown heterozygosity, 2 heterozygosity below 0.1 and unknown minor allele frequency (MAF) or MAF below 0.1 were excluded. Among 12 missense SNPs, 2 unknown heterozygosity, 1 unknown MAF, and 7 MAF below 0.1. Among 12 missense SNPs, SNPs with unknown heterozygosity or heterozygosity below 0.1 were 9 and SNPs