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Clinical significance of papillary thyroid cancer risk loci identified by genome-wide association studies

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Four single nucleotide polymorphisms (SNPs) have been reported to be associated with thyroid cancer risk in two genome-wide association studies (GWASs) and were validated in a Chinese population. Because of a lack of further clinical and functional evidence, the clinical significances of these SNPs remain unknown. Four GWAS-identified SNPs of papillary thyroid cancer (PTC), rs965513, rs944289, rs966423 and rs2439302, were genotyped in a case-control study of 838 patients with PTC and 501 patients with benign thyroid tumor (BTT) from the Chinese Han population. The associations between these SNPs, clinicopathologic features, and the outcome of the PTC patients were examined. The CT and CT + TT genotypes of rs966423 were more common in PTC patients with extrathyroidal extension and more advanced T stage. The TC and TC + CC genotypes and the C allele of rs944289 were significantly less frequent in patients with multifocal disease. No correlation was observed between GWAS-identified SNPs and disease persistence of PTC after a short-term follow-up. Significantly different allele distributions between the PTC and BTT groups were observed for all four selected SNPs. Individuals with more than five risk alleles were 8.84-fold (95% CI 3.23–24.17) more likely to suffer from PTC compared with those with zero or 1 risk allele. GWAS-identified SNPs affect the individual predisposition to PTC without interacting with existing Hashimoto thyroiditis and BTT lesions. GWAS-identified SNPs were associated with certain clinicopathologic features of PTC, and may contribute to identifying PTC patients with different clinical patterns. Large prospective studies are required to further evaluate the diagnostic and prognostic power of these genetic markers.

Keywords Papillary thyroid cancer, Genome wide association study, clinical significance, Chinese population

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Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, which is the fifth leading malignancy in female patients (1). Although it is widely accepted that both genetic and environmental factors contribute to PTC carcinogenesis, the etiology of this cancer is not well characterized (2). Among the genetic factors, only a few somatic mutations have been proven to drive tumorigenesis (3). On the other hand, the risk ratio of PTC in first-degree relatives of a PTC case is more than 8, which is one of the highest risk ratios in all types of malignancies (4), suggesting the great importance of genetic factors in PTC susceptibility. Accumulating evidence from epidemiological studies suggests that the genetic predisposition of patients to PTC may result from a series of low penetrance variants rather than several high penetrance genes (5–7).

Genome-wide association studies (GWASs) allow for the examination of a much wider range of genetic variants than do candidate-gene association studies. GWASs have provided an efficient approach to identifying common and low penetrance risk variants contributing to tumor susceptibility. The first GWAS of PTC was conducted in an Icelandic population (6). Two loci, located in chromosome 9q22.33

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(rs965513) and 14q13.3 (rs944289), showed highly significant associations with PTC. In a more recent study, the same research group reported three new loci (rs966423 on 2q35, rs2439302 on 8p12, and rs116909374 on 14q13.3) that were associated with thyroid cancer risk in another GWAS from a European population (7). In a validation study, four of these candidate loci were confirmed in a Chinese population (8).

In general, GWASs have enabled investigators to identify individual genetic predispositions to certain malignancies. However, the question of whether such a genetic background affects the clinical pattern of tumor progression, besides just participating in carcinogenesis like some other tumor risk–related single nucleotide polymorphisms (SNPs) (9), has been less studied. In fact, several SNPs identified by GWASs were found to have potential prognostic value in patients with colorectal cancer and breast cancer (10,11). To evaluate the clinical significance as well as the prognostic implications of PTC risk loci identified by GWASs, we analyzed associations between four SNPs (rs944289, rs965513, rs966423, rs2439302) and various clinicopathologic characteristics, including short-term disease persistence, in a Chinese population. The potential diagnostic value of these SNPs in distinguishing PTC cases from patients with thyroid nodules was also evaluated.

Materials and methods

Study participants

The study population consisted of 838 patients with PTC and 501 patients with benign thyroid tumor (BTT) who were treated at the Department of Head and Neck Surgery, Cancer Hospital, Fudan University, Shanghai, China, between January and December 2010; this population was briefly described in our previous report (8 PTC and five BTT cases were excluded because of incomplete clinical data or failed genotyping) (8). All subjects were ethnically Chinese Han and were from Eastern China. All patients had a confirmed histological diagnosis without previous medical treatment of thyroid disease or history of radiation exposure. This study was approved by the ethical committee of the Cancer Hospital, Fudan University, and informed consent was obtained from all participants.

Genotyping

Four GWAS-identified SNPs of PTC, which had previously been confirmed in a Chinese population, were genotyped. Genomic DNA was extracted from peripheral blood samples using the LifeFeng kit (Shanghai LifeFeng Biotechnology, Shanghai, China) according to the manufacturer's instructions. Genotyping was performed with the SNaPshot multiplex single nucleotide extension system (Thermo Fisher Scientific, Waltham, MA). Primers for PCR amplification were designed using the primer-designing software Primer Premier version 5.0 (Premier Biosoft International, Palo Alto, CA) according to the reference sequence from the SNP database (http://www.ncbi.nlm.nih.gov/snp/). All SNP loci were genotyped with the ABI PRISM V.3730 Genetic Analyzer and Peak Scanner software, V.1.0 (Thermo Fisher Scientific). Internal positive and negative control samples were employed for quality control.

Clinical management

The management of thyroid tumors in our center was described previously (12). In our hospital, all patients received an ultrasonography (US) examination prior to surgery. Fine needle aspiration (FNA) and CT scans were not performed routinely. Lobectomies with pathologic frozen section examination were routinely performed during the operations. If a malignant diagnosis by frozen-section analysis was reported intraoperatively, lymph node dissection and contralateral lobectomy were performed, based on the risk stratification of the tumor.

The following clinical features were included in the analyses: patient's gender, patient's age at diagnosis, tumor size, extrathyroidal invasion, multifocality, Hashimoto thyroiditis status (HT), paracancer BTT (PTC/BTT), serum thyroid-stimulating hormone (TSH) level, and central and lateral neck lymph node metastasis. Tumor size was measured at the largest diameter of the largest lesion. Extrathyroidal invasion of the primary tumor consisted of gross and microscopic extrathyroidal extension. Multifocal primary lesions were defined as two or more cancer sites within the thyroid gland. HT status was confirmed by microscope by a pathologist. PTC/BTT refers to coexisting PTC and BTT lesions within at least one lobe of the thyroid gland and BTT located nearby or surrounding the cancer site (13). TNM stage was defined as the reference outlined by the National Comprehensive Cancer Network (NCCN) guidelines for thyroid cancer (14).

Postsurgical radioactive iodine therapy was limited to patients who had distant metastases, because its use is strictly controlled in China. All PTC subjects received TSH-suppressive hormonal therapy after surgery. During the follow-up period, all patients were advised to receive US examination of the thyroid and neck every 3–6 months in the first year, 6–12 months in the 2–3 years after the operation and then annually if they were disease-free. Locoregional recurrence was diagnosed by US or CT plus FNA when needed.

Statistical analysis

Differences in selected variables and Hardy–Weinberg equilibrium were evaluated using the χ^2 test and *t* test as appropriate. The association between each SNP and clinicopathologic characteristics, as measured by the odds ratio (OR) and its 95% confidence interval (CI), was evaluated and adjusted by multivariate logistic regression analyses. In all analyses, the common homozygote genotype was defined as the reference category. A P value < 0.05 was considered statistically significant. All the statistical analyses were performed with SPSS Software, version 12.0 (IBM, Armonk, NY).

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