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Genotypic characteristics and their association with phenotypic characteristics of hereditary medullary thyroid carcinoma in Korea

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ABSTRACT

Background: Hereditary medullary thyroid carcinoma can present as a part of multiple endocrine neoplasia syndrome by rearranged during transfection gene mutation. We evaluated the prevalence of rearranged during transfection gene mutation in patients who have medullary thyroid carcinoma and the correlations of genotype with medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism according to the revised American Thyroid Association risk level.

Methods: A total of 331 patients were diagnosed with medullary thyroid carcinoma, 172 of whom were tested for the rearranged during transfection germline mutation by sequencing of exon 8, 10, 11, and 13–16. These patients were diagnosed during the years 1982–2012 at 2 Korean tertiary hospitals. Patients were analyzed according to the route of diagnosis (screened versus index cases) or the mutational site of rearranged during transfection gene (the American Thyroid Association risk group).

Results: Rearranged during transfection mutation was found in 23.8% of patients tested, showing a decreasing trend with time. The most commonly mutated codon was codon 634 (37.1%), followed by codon 918 (14.3%). rearranged during transfection–positive patients were younger than rearranged during transfection–negative patients, although no other clinicopathologic characteristics differed. Screened cases were younger and had smaller tumors than index cases. Among rearranged during transfection–positive patients, pheochromocytoma manifested in 35.1% and hyperparathyroidism in 7.0%. Notably, pheochromocytoma and hyperparathyroidism emerged at any time after the diagnosis of medullary thyroid carcinoma. The American Thyroid Association risk-group analysis demonstrated that medullary thyroid carcinoma patients in the highest risk group were younger, had larger tumors, and higher disease-specific mortality. Similar results for pheochromocytoma were found, according to the American Thyroid Association risk group, although the results were not significant.

Conclusions: Korean patients who have medullary thyroid carcinoma showed a similar distribution of rearranged during transfection gene mutation with those in Western countries. The American Thyroid Association risk classification was shown to be useful for pheochromocytoma, as well as for medullary thyroid carcinoma. Familial screening for rearranged during transfection mutation and lifelong monitoring for associated pheochromocytoma should be emphasized in hereditary medullary thyroid carcinoma.

Introduction

Medullary thyroid carcinoma (MTC) is an uncommon disease accounting for 3%–10% of all thyroid cancers[1,2]; it is rarely cured without complete surgical resection. Thus, it is important to de-

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tect tumors at an early stage to achieve complete resection or biochemical remission after surgery.[3–6] Because approximately 25% of MTC cases are known to be hereditary, screening for rearranged during transfection (*RET*) gene mutations has been emphasized in patients newly diagnosed with MTC or suspected as having a hereditary component to their MTC.[7] Since the introduction of *RET* genetic screening into clinical practice in 1993,[7,8] it has been increasingly used for the diagnostic screening of MTC to identify hereditary cases. It has been widely accepted that more than 100 *RET* gene mutations have been reported to cause hereditary MTC and the genotype–phenotype relationship according to the types of mutation of the *RET*; specifically, the clinical behavior or aggressiveness of MTC differs according to the mutated site of the *RET* gene.[7,9,10] Recently, the American Thyroid Association (ATA) revised the groups of *RET* gene mutations into 3 categories (moderate [MOD], high [HIGH], and highest [HST])[9] from the previous 4 categories,[10] based on the risk and timing of MTC development and the aggressiveness of the disease. Although a few studies previously supported the usefulness of the new ATA risk classification to evaluate the clinical course of MTC,[11,12] limited data were available about the clinical application of the new classification in Asians.

Pheochromocytoma accompanies MTC at a rate of up to 50% in patients with multiple endocrine neoplasia (MEN),[13] showing higher penetrance in cases with codon 634 mutation; it can be another major phenotype that influences morbidity and mortality. Furthermore, hyperparathyroidism accompanies MTC in approximately 30% of MEN patients.[9,14] However, it has remained unclear whether the aggressiveness or characteristics of combined pheochromocytoma or hyperparathyroidism differ according to the mutational status of the *RET* gene or the classification according to the new ATA risk groups.

In the present study, we aimed to evaluate the prevalence of *RET* germline mutation and clinicopathologic characteristics according to the *RET* gene mutation status in a relatively large number of Korean patients with MTC, whose clinicopathologic characteristics and long-term prognosis during a median of 4.5 years were available.[3] In addition, we validated the effects of *RET* gene mutation status using the revised ATA risk levels on the clinical phenotypes related to the mutation.

Materials and Methods

Patients

A total of 331 patients who were diagnosed with MTC and followed in the years 1982–2012 at Seoul National University (SNU) Hospital ($n = 165$) or Severance Hospitals ($n = 166$) in Seoul, Korea were analyzed.[3] Among the patients, 172 were tested for *RET* gene mutation (Fig. 1). Data on the family history of MTC and the presence of phenotypes of pheochromocytoma or hyperparathyroidism were obtained by reviewing the medical records. This revealed that there were 12 patients who were relatives of the other patients among the 172 *RET*-tested patients, although they had originally been diagnosed as independent index cases. Hereditary MTC was defined as cases showing any of the following characteristics: positivity for *RET* germline mutation (36 among 151 *RET*-tested family) and a family history of MTC or any combined phenotype of MEN2 syndrome such as pheochromocytoma and hyperparathyroidism even with no knowledge of the *RET* mutational status (5 among 159 *RET*-untested patients).[9,15] Sporadic MTC was considered if the patients showed none of the following characteristics; any *RET* gene mutation, familial history of MTC, and any combined phenotypes.[16] We divided the *RET*-positive patients into subgroups in terms of whether they had been diagnosed through familial screening (screened cases, $n = 11$) or by their apparent tumors (index cases, $n = 46$) to exclude the effects of screening for some analyses. We defined patients as index cases if they had been diagnosed by their apparent tumor not through familial screening.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of SNU Hospital (IRB No. H-1301-068-459) and Severance Hospitals (IRB No. 3-2013-0306).

Histopathologic examination

Pathology data of MTC, such as tumor size, extrathyroidal extension (ETE), and lymph node (LN) metastasis, were obtained based on the World Health Organization's International Histological Classification of Tumors.[17] Primary tumor diameter was determined by direct measurement of surgical thyroid specimens. When multiple MTCs were present, the characteristics of the largest tumor were used for the analysis. LNs were assessed based on positive or negative LNs, and nonresected LNs were categorized as negative LNs.

Pathologic reports were available in 18 of 20 pheochromocytoma cases and all 4 hyperparathyroidism cases. Tumor size of pheochromocytoma or parathyroid adenoma was also determined by direct measurement of surgical specimens, using the largest tumor dimension.

RET gene analysis

All patients with newly diagnosed MTC were recommended to undergo genetic testing for *RET* germline mutation (exons 8, 10, 11, and 13–16) as standard practice from 2008 in SNU Hospital, and from 2012 in Severance Hospital. This was also recommended to all patients followed during the study period, even if they underwent surgery before 2008 or 2012, respectively. Research-based genetic tests were also performed in some patients even before the these periods if there was strong evidence for a hereditary component to their MTC. Before undergoing genetic testing, all patients or their legal guardians provided written informed consent. We evaluated the frequency of *RET* gene mutations with time (before 2000, 2000–2007, and after 2007), considering the *RET* gene test as standard practice since after the year 2007.

Direct sequencing of DNA was performed using the AB 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) with the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems) in Severance Hospital. In SNU Hospital, ABI 3730 Genetic Analyzer (Applied Biosystems) since 2007, ABI 3130 Genetic Analyzer (Applied Biosystems) 2004– 2007, and PRISM 373A (Applied Biosystems) before 2004 were used for direct sequencing of DNA.

Follow-up measurements and definition of disease status

Measurement of preoperative serum calcitonin levels and neck ultrasound or computed tomography (CT) was carried out for most patients as previously described.[3] In brief, during postsurgical follow-up, measurement of serum calcitonin levels and neck ultrasound were carried out between 2 and 6 months after initial surgery, and then checked annually. Patients with hereditary MTC were screened for pheochromocytoma and hyperparathyroidism biochemically using a 24-hour urine catecholamine, serum calcium, and intact parathyroid hormone. Although these biochemical screening tests for pheochromocytoma were not performed in 17 patients, we considered that they did not have coexisting pheochromocytoma because they showed no such symptoms. When pheochromocytoma or hyperparathyroidism was diagnosed within 6 months before or after the diagnosis of MTC, the tumors were considered concomitant.

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