Genetic Approach to Thyroid Nodules and Cancer

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Thyroid tumors are responsible for most of the annual deaths caused by endocrine organ cancers and thyroid cancer (TC) is the third most common cancer in women in our country. 90% of these tumors originate from follicular cells and the rest originate from C cells producing calcitonin or other cell types. The anaplastic TC is the one with the worst course and yet it is the least seen type of TC. The mutations result in dysfunction of the *p53* gene which accompanies the anaplastic cancer of thyroid. Differentiated TC [papillary TC (PTC) and follicular TC (FTC)] progress slowly, permitting longer survival. 75% of the cases have PTC and 20% of the cases have FTC. Clonal mutations, which can identify the prognosis, can be detected at early stages of PTC or FTC. In PTC, 45% BRAF mutations can be seen. For most of the time, this mutation can be detected at early stages pointing a bad prognosis. Even though different mutations can be observed, V600E (T1799A) constitutes 90% of mutations. In 20% of PTCs, the fusion of the *PTC* gene with the *RET* gene is found in 10q11.2 and functioning in MAPK pathway is present, whereas 5 to 10% of cases have rearrangements of the neurotrophic tyrosine kinase receptor 1 (*NTRK1*) gene. Twelfth and 61st codon mutations of RAS family members (HRAS, NRAS and KRAS) are detected in 10-20% of cases. 50% of cases with FTC has RAS mutations (at NRAS the most). Other than that, *PAX-PPARγ1* fusion gene occurs as a result of t(2;3)(q13;p25) which is found in 35-45% of the FTC cases. This mutation is seen in early stages of carcinogenesis and the improvement of this process depends on the presence of other mutations. In addition to these, the loss of the *ARH1* gene or silencing of the gene with hypermethylation is important in progression from adenoma to carcinoma. Especially for metastatic TC, with the usage of receptor tyrosine kinase inhibitors (RTKi) with common effects or target treatment agents such as selective BRAF RTKi, the importance of molecular tests increases because of their role in the treatment choice. Hereditary TCs form 5% of all TC and they are usually medullary type. These usually appear as a component of multiple endocrine neoplasia known as MEN syndromes. MEN1 syndrome is seen very rarely and it is related to *MEN1* gene mutation located at 11q23. In familial MEN type 2, the mutations are found in the *RET* gene located at 10q11.2. The same mutations are identified in non-familial medullary TC (MTC). All familial forms of MEN type 2 (MEN2) and MTC show autosomal dominant inheritance. In almost all of MEN2A cases, MTC is present and it has been considered as a variant of MEN2A. *RET* oncogene mutations are detected in 95% of cases with MEN2A and similarly in 88% of MTC cases. The mutations especially found in the 10th, 11th and 13th exon coding the extracellular domain of the *RET* gene are related to MEN2A and MTC, whereas the mutations in the 14th-16th exons of the same gene are related to MEN2B. For MEN2B patients carrying mutations at codon 918 and codon 833 or 'compound' heterozygous patients (codons 804/805, 804/806, 804/904), it has been suggested to perform a prophylactic total thyroidectomy at either early periods of life or at the time of diagnosis. The patients who received hereditary MTC syndrome diagnosis sufficiently at an early time and the ones with mutations at codons 609, 611, 618, 620, 630, or 634 should be considered as possible candidates for a prophylactic thyroidectomy either at age 5 or at the time of identification of mutation. Because the lesser lethality is observed in patients with mutations at codons 768, 790, 791, 804 and 891, these patients are suggested to be followed up with annual US and basal calcitonin levels. RET mutations are detected in 6% of sporadic MTC cases. For this reason, all of the newly diagnosed sporadic MTC cases should be investigated for RET mutations and should be directed to genetic consultancy. The somatic mutations at the 11th, 13th and 16th exons are responsible for sporadic MTCs. Mutations on the *CDKN1B* gene localized at 12p13 are accounted for recently described MEN4 going together with parathyroid and pituitary tumors. Other than the ones described here, there are various different markers which are continued to be identified. With the knowledge growing on molecular genetics and technologic improvements, lots of different genes are identified playing a role in cancer development. The processes that administer the genes on the main pathways playing an essential role in cell cycle are now evaluated as pathway pathologies. Owing to the arrays and new generation sequence analysis, which provides high data and pace, developed within the last decade, all of these pathways could be investigated and these diagnostic tools will be used in short amount of time. These improvements will help doctors choose the right treatment at early stages of disease and to develop possible available personalized target treatments in the near future.

Key words: Thyroid cancer, MEN, *RET*, MTC, *RAS, BRAF, RTKi*