Novel Findings in Familial Nonmedullary Thyroid Cancer Genetics

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Editorial

Thyroid cancer (TC) is the most common endocrine malignancy and its incidence has been increasing sharply since the mid-1990s [1]. TC is a general term that comprises two main groups of neoplasias, depending on the cell type affected by the malignant transformation. 1) Carcinomas originating from the follicular epithelium, referred to as nonmedullary thyroid cancer (NMTC) representing more than 95% of all TC; and 2) carcinomas originating from the parafollicular thyroid C cells, referred to as medullary thyroid cancer (MTC) accounting less than 5% of all TC.

NMTC is prevalently sporadic, but evidence of a familial inheritance is accumulating over the last years with prevalence from 5-10% in different series [2]. Several large case control studies have reported the heritability of FNMTC to be one of the highest of all cancers [3]. Despite this fact, the genetic inheritance of FNMTC remains unknown, but it is believed to be autosomal with incomplete penetrance and variable expressivity [4]. Importantly, there is some controversy about the higher aggressiveness of FNMTC compared with its sporadic counterpart. However, higher incidence of tumor multifocality, local invasion, lymph node metastasis, and local or regional recurrences have been also observed when compared with the sporadic variant. In addition, FNMTC occurs at an earlier age, with some evidence suggesting genetic anticipation in successive generations [5].

On a molecular level, the genetic basis of FNMTC as a distinct syndrome remains poorly understood and the causative genes predisposing to FNMTC have not been yet identified. The variable expression of FNMTC suggests that the responsible gene(s) may lead to predisposition or susceptibility to thyroid cancer. Genetic analyses of large FNMTC kindreds not only support the hypothesis of an inherited genetic predisposition to FNMTC, but also represent the first steps in identification of the putative susceptibility genes. Five potential regions for harboring an FNMTC gene have been identified: MNG1 (14q32), thyroid carcinoma with oxyphilia (TCO) (19p13.2), fPTC/papillary renal neoplasia (PRN) (1q21), NMTC1 (2q21), FTEN (8p23.1–p22) [6]. Remarkably, all these studies showed the main limitation of being performed in individual families, with distinct variants of FNMTC, not existing in the vast majority of families. For that reason, some of these loci still remain to be confirmed in other families.

Recently, with the advent of new techniques in molecular genetics, four potential susceptibility loci for FNMTC have been identified using genome-wide association study (GWAS) technology and SNP array-genotype analysis [7,8]. In the first study, two common gene polymorphisms in two thyroid transcription factors were discovered, one in FOXE1 gene, and the other in the NKX2-1 gene [7]. The estimated risk of thyroid cancer in homozygous carriers was 5.7-fold greater than that of non-carriers. In the SNP array analysis [8], two new SNP markers on chromosomes 1q21 and 6q22 were found, possibly encompassing heretofore undiscovered genes that predispose to FNMTC.

Recently, the role of different microRNAs and the effect of telomeres and telomerases in the genetic predisposition to FNMTC have been investigated. MicroRNAs (miRNAs) are endogenous, conserved, single stranded, small (approximately 22 nucleotides in length), noncoding RNAs that repress gene expression at the post-transcriptional level by targeting mRNA [9]. In a recent study comparing the miRNA profile of FNMTC with their sporadically occurring counterparts [10], two miRNAs, miR-886-3p and miR-20a, were found to be differentially expressed by 3- and 4-fold by quantitative real time RT-PCR, respectively. In addition, miR-886-3p and miR-20a were also downregulated in NMTC as compared to normal thyroid tissue by approximately 4-fold. Furthermore, overexpression of miR-886-3p dramatic decreased the expression of genes that regulate DNA replication and focal adhesion in two different well-characterized thyroid cancer cell lines suggesting a potential tumor suppressor role for this miRNA [10]. On the other hand, miR-20a has been observed to promote cellular proliferation and invasion, and higher expression levels have been associated with tumor dedifferentiation in prostate and ovarian cancer among others [11].

Telomeres are non-coding regions at the end of eukaryotic chromosomes consisting of hundreds of copies of a simple tandem repeat sequence (TTAGGG in vertebrates) that serves to stabilize the chromosome. Telomeres progressively shorten with each cell replication due to incomplete lagging DNA strand synthesis and oxidative damage. Telomerase is a specialized ribonucleoprotein with reverse transcriptase activity that avoid telomere shortening by adding telomeric repeats to the G-rich strand [12]. The strong association of telomerase re-activation with cancer provides evidence that this mechanism plays an important role in cancer development. Moreover, in normal thyroid samples, telomerase activity (TA) is almost absent whereas among thyroid cancer, increased TA was found in all histotypes [13]. This issue was firstly reported in 1997, where the presence of TA was observed in 100% of FTC and absent in 76% of benign thyroid lesions [14]. Recently, it has been observed that FNMTC patients display shorter telomeres, increased amplification in hTERT gene copy number, and higher TA, compared with sporadic NMTC patients. These observations suggest that patients born with short telomeres might reach earlier in life the threshold telomere length sufficient to trigger cancer development and/or progression. Importantly, patients of the second generation were always diagnosed with thyroid cancer at an earlier age, compared with their affected relative in the first generation [15]. These findings are in agreement

with the definition of "genetic anticipation" reinforcing the hypothesis that FNMTC is a true familial disease rather than the fortuitous association of the same disease in a family.

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