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Editorial

An Overview of Thyroid Cancer Genetics and Inheritance

Thyroid cancer (TC) is the most common endocrine malignancy and its incidence hasbeen 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.

Although MTC accounts only for 5% of all the thyroid cancers, it is responsible forabout 15% of all the deaths related to thyroid cancer [2]. Familial medullary thyroid carcinoma (FMTC) encompasses about 25% of all the medullary thyroid carcinomas, appearing as part of a rare inherited syndrome called multiple endocrine neoplasia 2(MEN2) or as isolated FMTC. These familial forms have in common germline gain-of function mutations in the RET proto-oncogene, located on chromosome 10q1 1.2 [2]. Almost all patients with a germline RET mutation develop c-cell hyperplasia or MTC during their lifetime. Today, about 98% of all the mutations responsible for FMTC areknown.

Similarly, NMTC is prevalently sporadic, but evidence of a familial inheritance isaccumulating over the last years with prevalence from 5-10% in different series [3]. It isnamed as familial non-medullary thyroid carcinoma (FNMTC) and it is defined by thediagnosis of two or more first-degree relatives with thyroid cancer of follicular cellorigin without another familial syndrome. Several large case control studies have reported the heritability of FNMTC to be one of the highest of all cancers [4]. Unlike inthe case of MTC syndrome, caused by germline point mutations in the RET proto-oncogene; the causative genes predisposing to FNMTC have not been yet identified.

Regarding MTC, variations of the RET proto-oncogene and its effectors have monopolized the studies looking for low penetrance loci. MEN2 syndrome consists ofthree variants, MEN IIA, MEN IIB, and FMTC. This way, FMTC can occur in threedifferent manifestations [2].

FMTC: This form of medullary carcinoma is the least aggressive. This group of MTC patients usually develops no other clinical manifestations. Similarly to other types of thyroid cancers, the peak incidence is between the ages of 40 and 50 years.

MEN IIA (Sipple Syndrome): MEN IIA syndrome or Sipple syndrome presents bilateral medullary carcinoma or C-cell hyperplasia (CCH), pheochromocytoma, and hyperparathyroidism. This syndrome is inherited as an autosomal dominant manner, and males and females are equally affected. Peak incidence of medullary carcinoma in thesepatients is in the 30s, as late adolescence or early adulthood.

MEN IIB: It is associated with pheochromocytoma, mucosal ganglioneuromas, and marfanoid habitus. This syndrome also presents medullary carcinoma and pheochromocytoma, but only rarely will have hyperparathyroidism. Inheritance isautosomal dominant as in MEN IIA. MEN IIB patients usually get medullary carcinomaearly in life, diagnosed in infancy or early childhood before their 30s, and males andfemales are equally affected.

In contrast with MTC, the variable expression of FNMTC suggests that the responsiblegene(s) may lead to predisposition or susceptibility to thyroid cancer. With the adventof new techniques in molecular genetics, a number of potential loci for FNMTC geneshave been identified [5].

MNG1 14q31 locus: It was the first locus identified to be potentially implicated inFNMTC [6]. A Canadian pedigree with 18 cases of multinodular goiter (MNG) and 2 cases of NMTC were studied [6]. After genotyping 34 individuals, a potentialsusceptibility locus at 14q31 was identified. Linkage was not found in additional FNMTC pedigrees suggesting that this locus may account for only a minority of FNMTC cases with MNG.

TCO 19p132 locus: The thyroid tumors with cell oxyphilia (TCO) locus were mapped for the first time on chromosome 19p132 in a French family consisting of six cases of MNG and three of NMTC by the French NMTC Consortium [7]. Importantly, analysis of additional families has provided evidence for the genetic interaction between the TCO at 19p132 and NMTC1 at 2q21 loci (another potential genetic locus), resulting in a significantly increased risk of NMTC in patients carrying both susceptibility loci [8].

fPTC/PRN 1q21 locus: It was firstly identified on chromosome 1q21 in an American family with five members affected by PTC, one by colon cancer and two by papillaryrenal neoplasm (PRN) [9]. As far as we know, to date, the relationship of this locus with FNMTC has not been confirmed in any other independent study and no further families with a PTC and PRN association have been reported.

NMTC1 2q21 locus: The existence of the susceptibility locus NMTC1 for FNMTC onchromosome 2q21 was first identified in a large Tasmanian pedigree with recurrence of PTC [10]. As commented before, analysis in additional families suggest that alterations at TCO and NMTC1 could be important in a fraction of cases with FNMTC.

FTEN 8p23.1-p22 locus: It was discovered in a clinical screening of a Portuguese family with 11 cases of benign thyroid disease and 5 cases of thyroid cancer using higher genomic resolution techniques such as single-nucleotide polymorphism (SNP) followed by microsatellites [11]. A single region on chromosome 8p23.1-p22 of 7. 46-Mb span was found.

Remarkably, all these studies showed the main limitation of being performed inindividual 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. To address this limitation, genome-wide association study (GWAS) technology and SNP array-genotype analysis have been utilized, and four potential susceptibility loci have been identified [12,13]. 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 [12]. The estimated risk of thyroid cancer inhomozygous carriers was 5.7-fold greater than that of non-carriers. In the SNP arrayanalysis [13], two new SNP markers on chromosomes 1q21 and 6q22 were found, possibly encompassing here to fore undiscovered genes that predispose to FNMTC.

On the other hand, recent technical advances in molecular genetics, such as multiple germline mutation analyses have excluded the most common somatic mutations ingenes associated with sporadic thyroid cancers, including RET, RET/PTC, MET, MEK1, MEK2, APC, PTEN and NTRK, as candidate genes for FNMTC [11].

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