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.

Although MTC accounts only for 5% of all the thyroid cancers, it is responsible for about 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 10q11.2 [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 are known.

Similarly, NMTC is prevalently sporadic, but evidence of a familial inheritance is accumulating over the last years with prevalence from 5-10% in different series [3]. It is named as familial non-medullary thyroid carcinoma (FNMTCT) and it is defined by the diagnosis of two or more first-degree relatives with thyroid cancer of follicular cell origin without another familial syndrome. Several large case control studies have reported the heritability of FNMTCT to be one of the highest of all cancers [4]. Unlike the case of MTC syndrome, caused by germline point mutations in the RET proto-oncogene; the causative genes predisposing to FNMTCT 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 of three variants, MEN IIA, MEN IIB, and FMTC. This way, FMTC can occur in threecase manifestations [2].
NMTC 2q21 locus: The existence of the susceptibility locus NMTC1 for FNMTC on chromosome 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 746-Mb span was found.

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. 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 in homozygous 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 in genes associated with sporadic thyroid cancers, including RET, RET/PTC, MET, MEK1, MEK2, APC, PTEN and NTRK, as candidate genes for FNMTC [11].

Acknowledgements

Dr. Orenes-Piñero is supported by a postdoctoral contract from the Instituto Murciano de Investigaciones Biosanitarias Virgen de la Arrixaca, Universidad de Murcia (IMIB, Murcia, Spain).

References


