Biochimica et Biophysica Acta 1846 (2014) 468–476

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Familial nonmedullary thyroid cancer: Screening, clinical, molecular and genetic findings

Diana Navas-Carrillo [a], Antonio Ríos [a], José Manuel Rodríguez [a], Pascual Parrilla [a], Esteban Orenes-Piñero [b,*]

[a] Department of Surgery, Hospital Universitario Virgen de la Arrixaca, University of Murcia, Murcia, Spain
[b] Department of Biochemistry and Molecular Biology-A, Biomedical Research Institute (IMIB), Campus of Lorca, University of Murcia, Spain

ARTICLE INFO

Article history:
Received 26 May 2014
Received in revised form 29 August 2014
Accepted 3 September 2014
Available online 11 September 2014

Keywords:
Familial nonmedullary thyroid cancer
Screening
Susceptibility loci
Telomerase
miRNA

ABSTRACT

Thyroid cancer, the commonest of endocrine malignancies, continues increasing in incidence being the 5th more prevalent cancer among women in the United States in 2012. Familial thyroid cancer has become a well-recognized, unique, clinical entity in patients with thyroid cancer originating from follicular cells, that is, nonmedullary thyroid carcinoma. Hereditary nonmedullary thyroid cancer may occur as a minor component of familial cancer syndromes (familial adenomatous polyposis, Gardner's syndrome, Cowden's disease, Carney's complex type 1, Werner's syndrome, and papillary renal neoplasia) or as a primary feature (familial nonmedullary thyroid cancer [FNMTC]).

Although there is some controversy, some epidemiologic and clinical kindred studies have shown that FNMTC is associated with more aggressive disease than sporadic cases, with higher rates of multicentric tumours, lymph node metastasis, extrathyroidal invasion, and shorter disease-free survival. This way, preventing screening will allow earlier detection, more timely intervention, and hopefully improved outcomes for patients and their families. On the other hand, in the last years, an important number of genetic studies on FNMTC have been published, trying to determine its genetic contribution. However, the genetic inheritance of FNMTC remains unclear; but it is believed to be autosomal dominant with incomplete penetrance and variable expressivity. This paper provides an extensive overview of FNMTC from several points of view. Firstly, the impact of early detection on prognosis, secondly, the management and follow-up of FNMTC patients, and finally, the role of susceptibility loci, microRNAs (miRNAs) and telomerases in recently identified isolated cases of FNMTC.

Contents

Abbreviations: TC, Thyroid cancer; NMTC, Nonmedullary thyroid cancer; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; HTC, Hürthle cell thyroid cancer; ATC, Anaplastic thyroid cancer; FAP, Adenomatous polyposis of colon; FNAC, Fine-needle aspiration cytology; MNG, Multinodular goiter; TCO, Tumours with cell oxyphilia; PRN, Papillary renal neoplasm; FTEN, Familial thyroid epithelial neoplasia; SNP, Single-nucleotide polymorphism; FOXE1, Forkhead box protein E1; NKX2-1, NK2 homeobox 1; GWAS, Genome-wide association study; CDC6, Cell division control gene 6; PIP5K1C, Phosphatidylinositol-4-phosphate 5-kinase type-1 gamma gene; PXN, Paxillin; ZYX, Zyxin; RT-PCR, Retrotranscriptase-polymerase chain reaction; TERC, Telomerase RNA component; hTERT, Human telomerase reverse transcriptase; TA, Telomerase activity

* Corresponding author at: Department of Biochemistry and Molecular Biology-A, Biomedical Research Institute (IMIB), Campus of Lorca, University of Murcia, Avda. de las Fuerzas Armadas, s/n, Lorca, Murcia, Spain . Tel.: +34 968 381027.
E-mail address: eorenes@um.es (E. Orenes-Piñero).

http://dx.doi.org/10.1016/j.bbcan.2014.09.002
0304-419X/

1. Introduction

Thyroid cancer (TC) is the most common endocrine malignancy and its incidence has been increasing sharply since the mid-1990s, being the fastest-increasing cancers in both men and women in United States [1]. Increased medical surveillance, the effect of environmental factors and more sensitive diagnostic tests, such as ultrasound and confirmation via fine-needle aspiration, are thought to account for this increased incidence [2]. There is significant disparity in thyroid cancer incidence by gender. TC is more common in women (approximately 3:1 ratio) becoming the 5th more prevalent cancer among women [1]. Some investigators have suggested that the higher rate of papillary thyroid cancer in women may be due to reproductive, hormonal and dietary factors, but the molecular factors that account for gender disparity in thyroid cancer incidence are unknown [3].

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. There are four histologic subtypes of NMTC: papillary (PTC) (85%), follicular (FTC) (11%), Hürthle cell (HTC) (3%) and the anaplastic histotype (ATC) (1%) [4].

Histologically, PTCs are composed of well differentiated epithelial cells and can be distinguished by distinctive nuclear alterations including pseudoinclusions, grooves, and chromatin clearing (Fig. 1A). PTC incidence is remarkably high in developed countries, it is typically slow growing, and when it spreads it usually metastasizes to local lymph nodes [5]. On the other hand, FTC lacks the morphological nuclear features of PTC (Fig. 1B), which tends to be more aggressive and produces distant metastasis rather than lymph node invasion [6]. Although some PTC and FTC behave aggressively, the vast majority can be managed effectively. An important histologic variant of FTC is the oncocytic (Hürthle cell, oxyphilic) follicular carcinoma composed of eosinophilic cells repleted with mitochondria [7]. ATCs, the most uncommon form of NMTCs, are characterized by undifferentiated cells with high mitosis rate, necrotic areas, spindle-like cell morphologies as well as giant and occasionally squamous cells. ATC behaves very aggressively, rapidly invades adjacent tissues and is considered one of the most lethal human cancers [5].

NMTC is prevalently sporadic, but evidence of a familial inheritance is accumulating over the last years with prevalence from 5–10% in different series [8]. The first description of familial nonmedullary thyroid cancer was reported in 1955 by Robinson and Orr in monozygotic twins [9], and since then, numerous cases of FNMTC were reported until FNMTC was recognized as a distinct clinical entity [10]. It is named as familial non-medullary thyroid carcinoma (FNMTC) 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 FNMTC to be one of the highest of all cancers [11] (Fig. 2). FNMTC may occur as a minor component of familial cancer syndromes (Adenomatous polyposis of colon (FAP), Gardner's syndrome, Cowden's

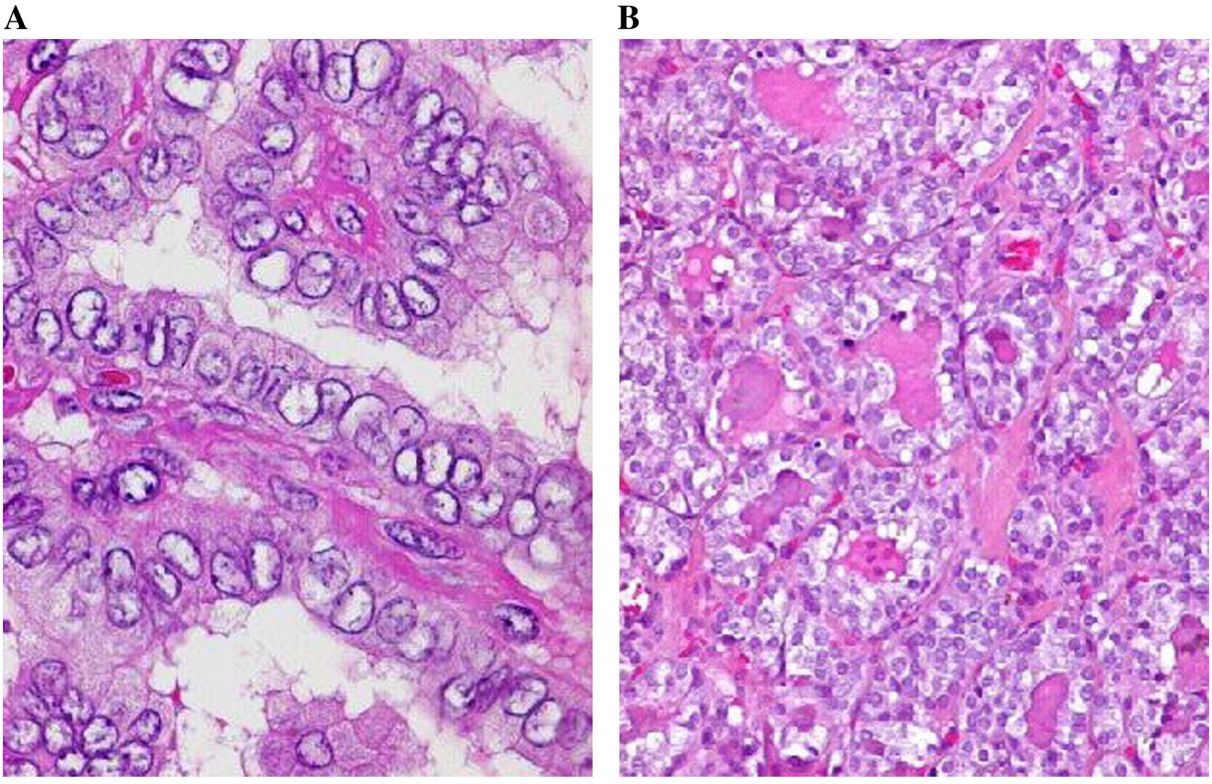

Fig. 1. Histopathology of the two differentiated subtypes of non-medullary thyroid neoplasias: A. Papillary thyroid cancer (PTC) characterized by distinctive nuclear alterations; B. Follicular thyroid cancer (FTC) without the morphological nuclear features of PTC.