Inherited Follicular Epithelial-Derived Thyroid Carcinomas: From Molecular Biology to Histological Correlates

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Abstract

Cancer derived from thyroid follicular epithelial cells is common; it represents the most common endocrine malignancy. The molecular features of sporadic tumors have been clarified in the past decade. However the incidence of familial disease has not been emphasized and is often overlooked in routine practice. A careful clinical documentation of family history or familial syndromes that can be associated with thyroid disease can help identify germline susceptibility-driven thyroid neoplasia. In this review, we summarize a large body of information about both syndromic and non-syndromic familial thyroid carcinomas. A significant number of patients with inherited non-medullary thyroid carcinomas manifest disease that appears to be sporadic disease even in some syndromic cases. The cytomorphology of the tumor(s), molecular immunohistochemistry, the findings in the non-tumorous thyroid parenchyma and other associated lesions may provide insight into the underlying syndromic disorder. However, the increasing evidence of familial predisposition to non-syndromic thyroid cancers is raising questions about the importance of genetics and epigenetics. What appears to be "sporadic" is becoming less often truly so and more often an opportunity to identify and understand novel genetic variants that underlie tumorigenesis. Pathologists must be aware of the unusual morphologic features that should prompt germline screening. Therefore, recognition of harbingers of specific germline susceptibility syndromes can assist in providing information to facilitate early detection to prevent aggressive disease.

Keywords Thyroid cancer · Familial non-medullary thyroid carcinoma · *APC* · *PTEN* · *SDHB* · *DICER1* · *PRKAR1A* · *WRN* · *RASAL1* · Cribriform-morular thyroid carcinoma · FAP · Cowden syndrome · PTEN-hamartoma tumor syndrome · DICER1 syndrome · Carney complex · Wermer syndrome

Introduction

A minor proportion of thyroid tumors is caused by germline susceptibility; within this group, these tumors derive from C cells (medullary thyroid carcinoma, MTC) or from follicular cells. While about 25% of MTCs are hereditary and their

genotype–phenotype relationship is well established, up to 10% of follicular epithelial-derived thyroid carcinomas are hereditary and their histological and molecular characteristics are much less well known [1–9]. Exceptionally, in some populations with many relatives living close together, a prevalence of up to 13.5% of inherited follicular cell derived

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carcinomas has been reported [10]. Inherited follicular epithelial derived thyroid carcinoma (TC) are usually referred to as familial non-medullary thyroid carcinomas (FNMTCs) and classified into two main subgroups depending whether the predominant cancer is the thyroid tumor (non-syndromic FNMTCs (NSFNMTCs)) or if it is a thyroid cancer that appears in a patient with a predominance of non-thyroid tumors (syndromic FNMTCs (SFNMTCs)) [9].

An important limitation in determining the true incidence of FNMTCs is related to the fact that follicular epithelial-derived thyroid carcinomas (including incidental papillary microcarcinomas) are common in the general population. A careful clinical documentation of family history or familial syndromes that can be associated with thyroid disease can help identify germline susceptibility-driven thyroid neoplasia. Thyroid neoplasms in three or more family member or the diagnosis of differentiated thyroid carcinoma with paternal inheriance in the proband may be a harbinger of inherited disease [11]. In addition, thyroid neoplasia can be the first clinically detected manifestation in some SFNMTCs as a significant number of patients with inherited FNMTCs also manifest with what appears to be sporadic disease. Therefore, detailed cytomorphologic assessment of thyroid nodules, application of molecular immunohistochemistry for relevant biomarkers, and careful assessment of the non-tumorous thyroid parenchyma can help diagnosticians in the detection of an inherited disease. From a clinicopathologic perspective, inherited follicular epithelial-derived thyroid carcinomas tend to have early onset disease with increased frequency of multifocal tumors that arise in the background of benign follicular nodular disease [11].

This article reviews the main characteristics of inherited follicular epithelial-derived thyroid carcinomas, emphasizing the genotype–phenotype correlations in a way that can be especially useful to pathologists for the recognition of the possible familial character of certain follicular cell-derived carcinomas in daily practice.

Non-Syndromic Familial Non-Medullary Thyroid Carcinoma (NSFNMTC)

To the best of our knowledge, in 1955 David Robinson and Thomas Orr published the first description of non-syndromic familial non-medullary thyroid carcinomas (NSFNMTCs) [12]; the patients, two identical 24-year-old twin sisters, showed several foci of classic papillary thyroid carcinoma (PTC) in their thyroid lobes and lymph node metastases. As was described in this prototypical first example, NSFNMTCs are usually PTCs (> 85%) characterized by an early onset, more bilaterality and multifocality and nodal metastases [10, 13–15].

Given the lack of distinctive histological features in this group of familial thyroid tumors, it has been proposed that the clinical diagnosis of NSFNMTC should be based on the evidence of PTC in two or more first-degree relatives, or on the finding of multinodular goiter (MNG) in at least three first- or second-degree relatives of a PTC patient, of course, always in the absence of previous ionizing radiation exposure and neoplasia syndromes [16, 17]. As secondary criteria the following have been proposed: the diagnosis in a patient younger than 33 years, multifocal or bilateral PTC, organ-exceeding tumor growth, metastasis, and familial accumulation of adolescent-onset thyroid disease [16]. Due to the general predominance of PTC in women, the diagnosis of PTC in a male, particularly in a young man, is also suggestive of a familial predisposition [18, 19]. Since the probability that it is not a sporadic carcinoma rises to more than 95% when three family members are affected [2, 20], the most recent studies suggest reserving the definition of NSFNMTC for all those cases with a minimum of three first-degree relatives diagnosed with follicular cell-derived thyroid carcinomas [3, 8, 10, 20, 21].

Patients with NSFNMTC tend to be younger than those with sporadic-non-medullary thyroid carcinoma (SNMTC) [3, 5, 14, 22–25], although not all series have found significant differences [1, 4, 6, 21, 26, 27]. Clinical "anticipation" with the second generation exhibiting the disease at an earlier age and having more advanced disease at presentation has been described in these families with NSFNMTC [7, 28], although the possibility of a bias due to more frequent evaluation in the familial group than in controls has been proposed [21]. Screening of at-risk family members resulted in earlier detection of low-risk FNMTC and was associated with a less aggressive initial treatment [29]. No significant differences in gender have been found between the sporadic and familial groups with thyroid carcinoma [10, 21].

Pathological Features

As previously mentioned, NSFNMTCs are primarily PTCs, both classical and follicular variants [10, 13, 19, 25, 28, 30–34], with more multifocality (with or without bilaterality) than in sporadic cases, usually in combination with benign lesions (hyperplastic nodules and/or follicular adenomas) [4, 10, 14, 22, 23, 26, 31–33, 35–39] (Fig. 1). Oncocytic change can also occur in these thyroid lesions [13, 40–43]. Synchronous PTC with follicular thyroid carcinoma (FTC), Hürthle cell carcinoma (HCC), and/or MTC have been occasionally reported [33].

Whether NSFNMTC is a more aggressive tumor remains a controversial issue. Compared with SNMTC, NSFNMTC is associated with a higher rate of lymph node metastases [3, 14, 28, 31, 38, 39], including lateral neck lymph node metastases [10] and Hashimoto's thyroiditis [39]. NSFNMTC was also associated with extrathyroidal extension [14, 27, 38, 39] and recurrence [14, 44]. Aggressive features,

Fig. 1 Non-syndromic familial non-medullary thyroid carcinoma case. Macroscopic appearance is not usually different from multinodular goiter (**a**). Histologically there is a combination of benign lesions (hyperplastic nodules as well as follicular adenomas) (**b**, **c**, **e**) with malignant follicular tumors. In this particular case, two papillary carcinomas can also be seen (**d**, **f**)
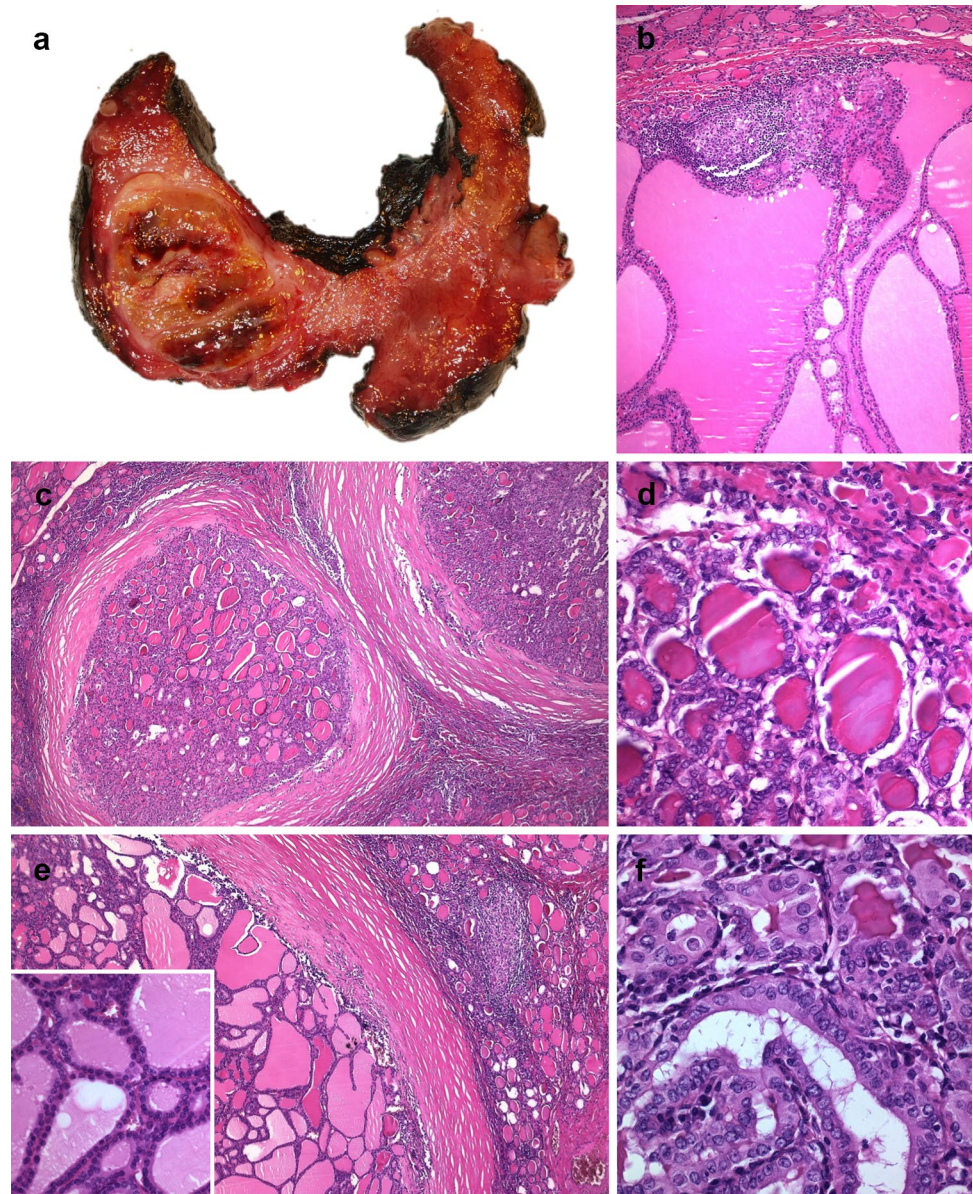
however, were most apparent in certain families with three or more affected members [21, 23, 27, 45]. Nevertheless, several studies found no differences in the clinical behavior and outcome between sporadic and NSFNMTC [1, 2, 6, 14]. Therefore, a recent study concluded that although NSFN-MTC is not more aggressive than SNMTC, this may not apply for the cases with three or more-affected relatives [21].

The usual coexistence of NSFNMTC with follicular nodular disease (including follicular epithelial cell hyperplasia to follicular adenoma progression sequence) suggests a multi-step process of tumor progression [23, 36], which together with its frequent multifocality justifies total thyroidectomy as the treatment for cases of NSFNMTC [10, 25, 26, 41]. Consistent with the current understanding of dynamic risk stratification in thyroid cancer, some studies indicate that familial papillary thyroid microcarcinoma is less aggressive than PTC greater than 1 cm and that a less invasive surgical treatment could be considered [46].

Genetic Features

NSFNMTC is genetically heterogeneous and poorly understood [13, 32, 47–50]. A recent whole-genome sequencing of NSFNMTC identified germline alterations that highlighted the central role of PI3K/AKT and MAPK/ERK signaling pathways in this type of thyroid cancer [51]. The reported genes and loci associated with NSFNMTC are summarized in Table 1.

Although some studies support the involvement of germline *FOXE1/TTF-2* (9q22.23) variants [52–54, 82], this

Table 1 Non-syndromic familial non-medullary thyroid carcinoma

Chromosomal loci (*designation*)	Gene	Thyroid lesions	Somatic thyroid tumor mutations	Additional lesions
9q22.23 [52–54]	*FOXE1*	PTC, FTC	*BRAF*[V600E] [54]	
14q13.3 [55, 56]	*NKX2-1*	PTC, MNG		
12q14.2 [57]	*SRGAP1*	PTC		
15q23 [58]	*MAP2K5*	PTC		
20p12.3 [59–61]	*PLCB1*	PTC (follicular variant), MNG (papilloid adenomata)		
10q25.3 [62, 63]	*HABP2*	PTC, FTA		
1q41 [64]	*BROX*	PTC (classical and follicular variant)		
7q31.33 [65–68]	*POT1*	PTC (classical and follicular variant), HCC, HCA, MNG		Melanoma, dysplastic nevi
19q13.33 [69]	*NOP53*	PTC, HCC		
22q12.1 [70]	*CHEK2*	PTC	*BRAF*[V600E] [70, 71]	Breast cancer [72]
19p13.11 [43]	*NDUFA13*	PTC (Hürthle cell variant), multiple Hürthle cell nodules		
19p13.2 [73]	*TIMM44*	PTC (classical and Hürthle cell variant), HCC, FTA with variable cell oxyphilia, multiple Hürthle cell nodules		
4q21.21 [74]	*ANXA3*	PTC (classical and follicular variant), HCC		
12q22 [74]	*NTN4*	PTC (classical and follicular variant), HCC		
14q32.13 [74]	*SERPINA1*	PTC		
17q21.2 [74]	*FKBP10*	PTC (classical and follicular variant)		
1p36.31 [74]	*PLEKHG5*	PTC (classical and follicular variant)		
17p13.2 [74]	*P2RX5*	PTC (classical and follicular variant)		
6p21.33 [74]	*SAPCD1*	PTC (classical and follicular variant)		
19p13.2 (*TCO/TCO1*) [13, 40–42, 75]	Unknown	PTC (classical and Hürthle cell variant), HCC, FTA with variable cell oxyphilia, multiple Hürthle cell nodules	19p13.2 LOH [76]	
8q24 (*PTCSC1*) [77]	Unknown	PTC, MNG, AITD		Melanoma
6q22 [33]	Unknown	PTC(classical and follicular variant), FTC#, HCC#, MTC#		
1q21 (*fPTC/PRN*) [33, 78]	Unknown	PTC, MNG		Papillary renal neoplasia [78]
14q32 (*MNG1*) [79]$	Unknown	PTC, MNG		
2q21 (*NMTC1*) [42, 75, 80]	Unknown	PTC (follicular variant)	2q21 LOH [75]	
8p23.1-p22 (*FTEN*) [81]	Unknown	PTC (classical and follicular variant), FTA, MNG	*BRAF*[V600E] [81]	

PTC papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *HCC* Hürthle cell carcinoma, *HCA* Hürthle cell adenoma, *FTA* follicular thyroid adenoma, *MNG* multinodular goiter, *AITD* autoimmune thyroid disease (Graves disease and Hashimoto's thyroiditis)

#Concurrent FTC, HCC, and medullary thyroid carcinoma (MTC) was found in 3 classical PTC cases

$At least some cases are probably secondary to germline *DICER1* gene mutation

association is not entirely consistent [83–85]. Nuclear FOXE1 immunoexpression in tumor cells in the vicinity of the PTC border is associated with the presence of a risk allele of rs1867277 (c.-238G>A) in the 5′ untranslated region of the *FOXE1* gene, as well as with pathological characteristics (multifocality and capsular invasion)

of PTC, suggesting possible FOXE1 involvement in the facilitation of tumor development [86].

Both *NKX2-1/TTF-1* (14q13.3) and *FOXE1* have been associated with the increased risk of sporadic PTC in Japan [82]. The *A339V NKX2-1* mutation may be a susceptibility gene for MNG and PTC [55], but this association could not

be replicated in another NSFNMTC study [87]. Although association between the 14q13 locus and a predisposition to a Chinese familial form of MNG with PTC have been reported in a more recent study [56], further validation studies are required to demonstrate the clinical usefulness of testing this gene mutation in NSFNMTC cases.

SRGAP1 (12q14.2) gene has been identified as a susceptibility gene in families with PTC [57]. The Q149H and R617C variants in *SRGAP1* could lead to a loss of function of the small G-protein CDC42 [57].

Recurrent genetic mutation of *MAP2K5* (15q23) variants c.G961A and c.T1100C (p.A321T and p.M367T) have been identified as susceptibility loci for NSFNMTC in Chinese families with PTC [58]; these mutations may result in an alternative activation of MEK5-ERK5 pathway in the MAPK signaling pathway.

The intronic *PLCB1* InDel is the first variant found in familial multiple papilloid adenomata-type MNG patients with more likelihood of progression to PTC and also found in a subset of patients with sporadic MNG [59, 60]. The InDel may contribute to MNG development through overexpression of phospholipase C beta 1 (PLCB1) (20p12.3) [60]. In this familial MNG of adolescent onset, the enlarged thyroid gland showed multiple nodules in a thyroid background of normal appearance. The nodules are sharply demarcated from the normal thyroid and are formed by follicles lined by follicular cells with small round regular nuclei and micropapillary projections [59–61]. This condition is different from the common MNG where the ill-defined nodules show large colloid rich follicles, and the background thyroid shows similar but less marked changes [61].

The pathogenic *HABP2* G534E variant has been associated with NSFNMTC [62, 63]. In addition, increased HABP2 protein expression in tumor samples from affected family members when compared with normal adjacent thyroid tissue and samples from sporadic cancers has been confirmed. [62]. Functional studies have shown that HABP2 has a tumor suppressive effect, whereas the G534E variant results in loss of function [62]. However, the role of the *HABP2* (10q25.3) gene in NSFNMTC is controversial [88–90] because the pathogenicity of *HABP2* variants in NSFNMTC could not be confirmed in Chinese, Brazilian and European studies [90–100]. Neither does this variant appear to play a role in sporadic PTC [101].

A new loss-of-function variant in *BROX* gene at 1q41 has been associated with the development of familial PTC (classical and follicular variants) [64], but more studies are needed to confirm this association. According to these researchers, *BROX* haploinsufficiency would induce altered EGFR degradation pathway in follicular cells, with EGFR accumulation and aberrant cell growth. [64].

POT1 (protection of telomeres 1) gene is located at 7q31.33. Germline mutation in *POT1* has been reported in a melanoma-prone family with thyroid cancer and MNG [65, 66], as well as in a family affected solely by NSFNMTC [68]. Thyroid lesions included PTC, benign and malignant Hürthle cell neoplasms and MNG [65, 66, 68]. Loss-of-function or reduced activity of *POT1* seems to play a pathogenetic role via dysregulation of telomere protection [68]. However, a lack of mutations in the *POT1* gene in selected families with NSFNMTC, with at least three affected members, has been reported in another recent study [102].

NOP53 gene, located in 19q13.33, encodes a nucleolar protein involved in ribosome biogenesis. The germline variant p. Asp31His in *NOP53* gene has recently been reported associated with NSFNMTC [69]. The patients had PTC and Hürthle cell carcinoma in one case, sometimes coexisting with MNG, including toxic MNG in two of the 11 affected members of the three families studied. Tumor tissue showed a higher immunohistochemical expression of NOP53 compared to the adjacent normal thyroid tissue in all four cases studied. [69].

CHEK2 variants may be associated with NSFNMTC [70, 72, 103]. *CHEK2* (22q12.1) gene mutations may contribute to tumorigenesis through the haploinsufficiency mechanism due to low CHEK2 protein levels [70]. In fact, a lower intensity of nuclear immunostaining for CHK2 protein has been detected in PTC cases with the *CHEK2* Y139X variant than in sporadic PTC cases [70]. A germline *CHEK2* mutation has been found in seven of 11 women (63%) with multiple primary cancers of the breast and thyroid [72]. Rare missense variants (R180C and H371Y) in cell cycle checkpoint kinase 2 (*CHEK2*) have also been identified in 2% of patients in a series of sporadic PTC [70]. Coexistence of *CHEK2* and *BRAF*V600E mutations has been reported in 10.8% of 427 unselected PTC patients, including mainly cases of the classical variant, but also of the follicular, oxyphilic, diffuse sclerosing, and solid variants [71]. In the same series, the coexistence of both mutations, however, was not associated with more aggressive clinicopathological features of PTC, poorer treatment response, or disease outcome.

Benign and malignant thyroid tumors with an oncocytic phenotype have been associated with germline [43] and somatic mutations [43] in the *NDUFA13/GRIM-19* (19p13.11) gene. Another group of familial oxyphilic (oncocytic) thyroid tumors has been associated with the *TCO* (thyroid tumors with cell oxyphilia) gene, which has been mapped to chromosome 19p13.2 [13, 40–42, 75]. Interestingly, a systematic screening of candidate genes mapping to the region of linkage in affected *TCO* members, led to the identification of novel germine changes in the *TIMM44* (19p13.2) gene [73]. In the same chromosomal region (19p13.2), a germline *KEAP1* gene mutation has been reported in a Japanese family with MNG but not thyroid cancer [104].

Mainly based on linkage analysis several susceptibility loci for NSFNMTC have been also proposed (Table 1).

A *PTCSC1* (papillary thyroid carcinoma susceptibility candidate 1) gene in 8q24 as a candidate gene for PTC predisposition was identified through linkage, haplotype sharing, and gene expression analysis in families with PTC, MNG, autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis), melanoma and other malignancies [77]. This association between 8q24 and risk for thyroid cancer and other cancers (prostate cancer, colorectal cancer, breast cancer, etc.), has been confirmed in recent studies [105, 106].

Linkage was identified with 2 single-nucleotide polymorphism markers on chromosomal loci 6q22 and 1q21 in families with classical and follicular variant of PTC (in some cases coexisting with FTC, HCC, or MTC) and FTC [33]. Interestingly, *FPTC/PRN* (familial PTC/papillary renal neoplasia) gene has also been mapped to 1q21 region in families with PTC, MNG, as well as, benign and malignant renal papillary neoplasms [33, 78].

Locus 14q (*MNG1* (multinodular goiter 1)) has been described as a susceptibility gene in families with adolescent-onset goiter, PTC and FTC [79]. Based on the chromosomal location and the type of lesions (multinodular goiter in childhood, beningn thyroid tumors, differentiated thyroid cancer, rhabdomyosarcoma, as well as ovarian and brain tumors) described in these families [79], we think that at least some cases are secondary to germline *DICER1* gene mutation [107] (see *DICER1* syndrome below). Loci Xp22 (*MNG2*) [108, 109] and 3q26.1-q26.3 (*MNG3*) [110] have been also associated with cases of familial non-toxic multinodular thyroid goiter but not with NSFNMTC.

A susceptibility locus 2q21 (*NMTC1* (non-medullary thyroid carcinoma 1) gene) has been found in a large Tasmanian family with PTC (follicular variant) and no cell oxyphilia or renal cancer [80]. There is also evidence that *NMTC1* (2q21) and *TCO* (19p13.2) may interact to increase risk in individuals that inherit both susceptibility genes [42, 75].

Another familial thyroid neoplasia susceptibility locus on 8p23.1-p22 called *FTEN* (familial thyroid epithelial neoplasia) has been described in a large Portuguese family with benign thyroid lesions and PTC [81].

An ultra-rare mutation (4q32A.C) involved in the predisposition to both PTC and ATC has been reported in a family with non-medullary thyroid cancer [111]. This mutation is located in a long-range enhancer element whose ability to bind the transcription factors *POU2F* and *YY1* is significantly impaired, with decreased activity in the presence of the C-allele compared with the wild type A-allele. An enhancer RNA is transcribed in thyroid tissue from this region and is greatly downregulated in NSFNMTC [111].

A recent study from Brazil also identified seven novel germline variants in familial PTC; these include p.D283N*ANXA3*, p.Y157S*NTN4*, p.G172W*SERPINA1*, p.G188S*FKBP10*, p.R937C*PLEKHG5*, p.L32Q*P2RX5*, and p.Q76*SAPCD1* [74].

The *BRAF*^{V600E} mutation is not a germline mutation in NSFNMTC [112]; however, *BRAF*^{V600E} [54, 70, 71, 81] as well as *HRAS* and *NRAS* [81] somatic mutations have been found in some cases of NSFNMTC, raising the possibility of mutations in DNA repair genes that prevent these sporadic mutations.

Syndromic Familial Non-Medullary Thyroid Carcinoma (SFNMTC)

In this group, the FNMTC is associated with syndromes having extrathyroid manifestations [9, 49, 113–115] (Table 2). The well-defined familial syndromes that are closely linked to FNMTC include familial adenomatous polyposis (FAP) syndrome, PTEN-hamartoma tumor syndrome, DICER1 syndrome, Carney complex, and Werner syndrome; however, patients with MEN1 syndrome [118] Marfan syndrome [119] and familial paraganglioma syndromes caused by *SDHx* mutations [120] can also manifest with thyroid follicular epithelial-derived neoplasia. It is not clear if the association with papillary thyroid microcarcinomas in multiple endocrine neoplasia type 2A (MEN2A) patients is related to specific germline changes of the *RET* gene or is reflective of how carefully the thyroids of MEN2A patients are examined [121, 122]. Recognition of these syndromes is important so that cancer screening and genetic counseling can be initiated. Pathologists also play an important role in recognizing the syndromes addressed below [123–125]. Given the well established genotype–phenotype correlations, this section will focus on well-defined thyroid neoplasia-related familial syndromes.

Familial Adenomatous Polyposis (FAP) Syndrome

FAP is an autosomal dominant syndrome caused by inactivating germline *APC* gene mutations and characterized by multiple colorectal adenomatous polyps and a high risk of colorectal, thyroid and other cancers [126]. *Classic FAP* is usually associated with the development of numerous (hundreds to thousands) colorectal adenomatous polyps and a nearly 100% risk of developing colorectal adenocarcinoma [127]. *Attenuated FAP* is characterized by fewer (20–100) adenomas in the large bowel, as well as both a slightly lower risk and later onset of colorectal cancer [128]. FAP also correlates with extracolonic lesions including congenital hypertrophy of the retinal pigment epithelium (CHRPE) [129], desmoid tumors [130], gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [131], duodenal [132] and hepatobiliary tree tumors, hepatoblastoma, adrenocortical adenomas and carcinomas, osteomas, epidermal cysts,

Table 2 Syndromic familial non-medullary thyroid carcinoma

Syndrome (inheritance)	Gene (gene location)	Thyroid lesions (incidence)	Main additional lesions
Familial adenomatous polyposis (autosomal dominant)	*APC* (5q22.2)	Cribriform-morular variant of TC (16%)	Colorectal adenomatous polyps, colorectal adenocarcinoma, CHRPE, desmoid tumors (GAPPS)
PTEN-hamartoma tumor syndrome (autosomal dominant)	*PTEN* (10q23.31)	MNG (43–75%) FTA (25%), HCA, lipoadenoma, and microadenomas PTC (microcarcinoma, classical and follicular variant) (60%) FTC (14–45%) HCC (≈ 1%) ATC (< 1%) C-cell hyperplasia Lymphocytic thyroiditis (55%)	Adult Lhermitte-Duclos disease[P]*, mucocutaneous lesions (facial trichilemmomas[P], papillomatous papules[P], acral keratosis[P]), autism spectrum disorder[P], breast cancer[M], macrocephaly[M], endometrial carcinoma[M], mucocutaneous lesions (multiple palmoplantar keratosis[M], multifocal cutaneous facial papules[M], macular pigmentation of the glans penis[M], multiple gastrointestinal (GI) hamartomas[M] or ganglioneuromas[M], FTA[m], MNG[m], single GI hamartoma[m] or ganglioneuroma[m], fibrocystic breast disease[m], lipomas[m], fibromas[m], genitourinary tumors (particularly kidney carcinoma)[m], genitourinary malformations[m], uterine fibroids[m], autism spectrum disorder[m]
DICER1 syndrome (autosomal dominant)	*DICER1* (14q32.13)	TC (PTC, FTC, PDTC) (rare)** FTA MNG	Pleuropulmonary blastoma, pulmonary cysts, cystic nephroma, Sertoli-Leydig cell tumor, gynandroblastoma, juvenile granulosa cell tumor, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, central nervous system sarcoma, presacral malignant teratoid tumor
Carney complex (autosomal dominant)	*PRKAR1A* (17q24.2)	TC (FTC, PTC) (15%) FTA MNG	Pigmentation in skin and mucosa (lips, conjunctiva and inner or outer canthi, penile and vaginal mucosa), multiple myxomas (cutaneous, mucous, cardiac and/or in the breast), primary pigmented nodular adrenocortical disease, large-cell calcifying Sertoli cell tumors, growth hormone-producing pituitary adenoma, blue nevus, epithelioid blue nevus, breast ductal adenoma, osteochondromyxoma
Werner syndrome (autosomal recessive)	*WRN* (8p12)	TC (18%) (FTC, PTC, ATC) FTA	Premature graying and/or thinning of scalp hair, bilateral ocular cataracts, deep, chronic ulcers around the ankles, short stature, melanoma, meningioma, soft-tissue sarcomas, leukemia and preleukemic disorders, osteosarcomas

TC thyroid cancer, *CHRPE* congenital hypertrophy of the retinal pigment epithelium, *GAPPS* gastric adenocarcinoma and proximal polyposis of the stomach, *MNG* multinodular goiter, *FTA* follicular thyroid adenoma, *HCA* Hürthle cell adenoma, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *HCC* Hürthle cell carcinoma, *ATC* anaplastic carcinoma

*P, pathognomonic criteria; M, major criteria; m, minor criteria; according to the International Cowden Consortium operational diagnostic criteria [116]

**There is a 16- to 24-fold increased risk of TC [117]

and extranumerary teeth [133]. *Gardner syndrome* is an obsolete term, and its use is not recommended since almost all FAP patients have these characteristics [126]. Although the association of FAP and brain tumors, commonly medulloblastomas, is referred to as *Turcot syndrome*, most cases are actually due to constitutional pathogenic mutations affecting the DNA mismatch repair genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2* [126].

The thyroid tumor associated with FAP is the cribriform-morular variant of PTC, more recently designated as cribriform-morular variant of thyroid carcinoma [134, 135]. The prevalence of the cribriform-morular variant (C-MV) of TC among FAP patients reaches up to 16% when ultrasonographic screening is combined with fine needle aspiration biopsy (FNAB) [136], and this is more common in young women (mean age 26 years, range 8–61 years, with a ratio women/men of 61:1, respectively) [134, 137, 138]. In these families the diagnosis of C-MV of TC precedes that of FAP in up to 40% of the cases [134]. Patients are generally euthyroid and C-MV of TC is sonographically more like a follicular tumor or MNG rather than PTC [134, 137]. Compared with sporadic cases, C-MV of TC associated with FAP are usually multifocal (and bilateral) tumors [134, 137].

Pathological Features

Although to the best of our knowledge, Crail reported the first case of C-MV of TC in a patient with FAP [139], it was Harach HR et al. who highlighted the peculiar microscopic characteristics of FAP-associated follicular cell-derived thyroid carcinoma, which usually presents as a multifocal and/or bilateral tumor [140]. Because of its distinctive histological features, Cameselle-Teijeiro and Chan proposed the term "cribriform-morular variant of PTC" and reported apparently-sporadic tumors which, unlike the syndromic type, usually appear as a single nodule [141].

C-MV of TC usually presents as a solid, white, fleshy, encapsulated, or well-defined nodule, partially divided into lobes by fibrous septa [134, 140, 141]. Histologically, there is a mixture of papillary, follicular, cribriform, trabecular, and morular (squamoid) growth patterns (Fig. 2a-f) Pseudopapillary and non-branched papillary structures are lined by cuboidal or columnar cells. The tumors, including areas of follicular and cribriform patterns, are usually devoid of colloid. In the solid areas there are oval to plump spindle cells and morules with aggregates of biotin-rich nuclei with a peculiar chromatin clearing. The tumor cells have abundant eosinophilic cytoplasm and the nuclei are usually hyperchromatic with a variable presence of nuclear features of PTC such as pallor, nuclear grooves, intranuclear cytoplasmic inclusions, and overlapping. The mitotic activity is generally less than 5 per 10 high power fields. Necrosis is uncommon. Capsular invasion and vascular invasion have

been reported in about 40% and 30% of cases, respectively. Psammoma bodies are not frequent [134]. Although the cribriform pattern of growth formed by anastomosing arches of tumor cells with non-fibrovascular stroma and morules are characteristic of C-MV of TC, a variable proportion of different patterns of growth can be found even among different tumors of the same patient. Adenoid cystic carcinoma-like areas have been reported in one case [142]. C-MV of TC with poorly differentiated features has also been reported [143].

Tumor cells are negative or focally positive for thyroglobulin (Fig. 2d) but always positive for TTF1 (Fig. 2f), and always negative for calcitonin and cytokeratin 20. Nuclear and cytoplasmic positivity for β-catenin is the hallmark of the C-MV of TC, in contrast to the membranous pattern in normal follicular cells. This is the only thyroid tumor with both nuclear and cytoplasmic positivity for β-catenin [134] (Fig. 2e). The role of LEF-1 as a marker of this TC still needs confirmation [144]. Tumor cells are also immunoreactive for keratins using the pankeratin clone AE1/AE3, low molecular weight keratin clone CAM5.2, and clone 34βE12 that identifies cytokeratins 1, 5, 10, and 14; they express epithelial membrane antigen, E-cadherin, vimentin, galectin-3, BCL-2, and p27 and are stained by the Hector Battifora mesothelial cell-1 (HBME1) antibody. Strong positivity for progesterone receptors and for α and β-estrogen receptors, as well as focal positivity for androgen receptors is usually detected [134]. Morulae are distinct from squamous metaplasia; the morules show nuclear positivity for β-catenin, are selectively positive for CDX2, CA19.9, and CD10, and are negative for TTF1, thyroglobulin, calcitonin, vimentin, and BCL2 [134, 145, 146].

Because of the morphological features of C-MV of TC, distinction from other primary or metastatic lesions may be necessary [147]. C-MV of TC can simulate a colonic or metastatic breast carcinoma, but positivity for TTF1 can help determine the correct diagnosis. The lack of morular structures, positivity for thyroglobulin and negativity for nuclear β-catenin distinguish columnar cell variant of PTC from C-MV of TC. Solid areas in the C-MV of TC can simulate a poorly differentiated thyroid carcinoma, but coexistence with a cribriform and/or morular pattern together with a lower mitotic index are typical of the C-MV of TC [147]. On the other hand, lung metastasis from C-MV of TC should not be misinterpreted as a primary adenocarcinoma of the lung based exclusively on the positivity for CK7 and TTF1 [148] can be helpful in this situation.

FNAB samples from C-MV of TC are commonly indicative of thyroid carcinoma, showing hypercellularity, papillary structures, epithelial flat monolayers, and/or morular structures [134, 137, 146, 147]. Tumor cells are tall and

Fig. 2 Cribriform-morular variant of thyroid carcinoma. This tumor is usually encapsulated or well-defined, partially divided by fibrous septa. Histologically, there is a mixture of cribriform (**a**), papillary (**c**), follicular, trabecular (**b**) or morular (squamoid) (**a**–**c**) patterns. Papillary or pseudopapillary structures are lined by cuboidal or columnar cells (**c**). Follicular and cribriform areas are usually devoid of colloid (**a**, **c**, **d**). Tumor cells are usually negative for thyroglobulin; focal positivity may represent trapped nontumorous tissue (**d**). Tumor cells are always positive for TTF1 (**f**). Nuclear and cytoplasmic positivity for β-catenin is the hallmark of the cribriform-morular variant of thyroid carcinoma (**e**)
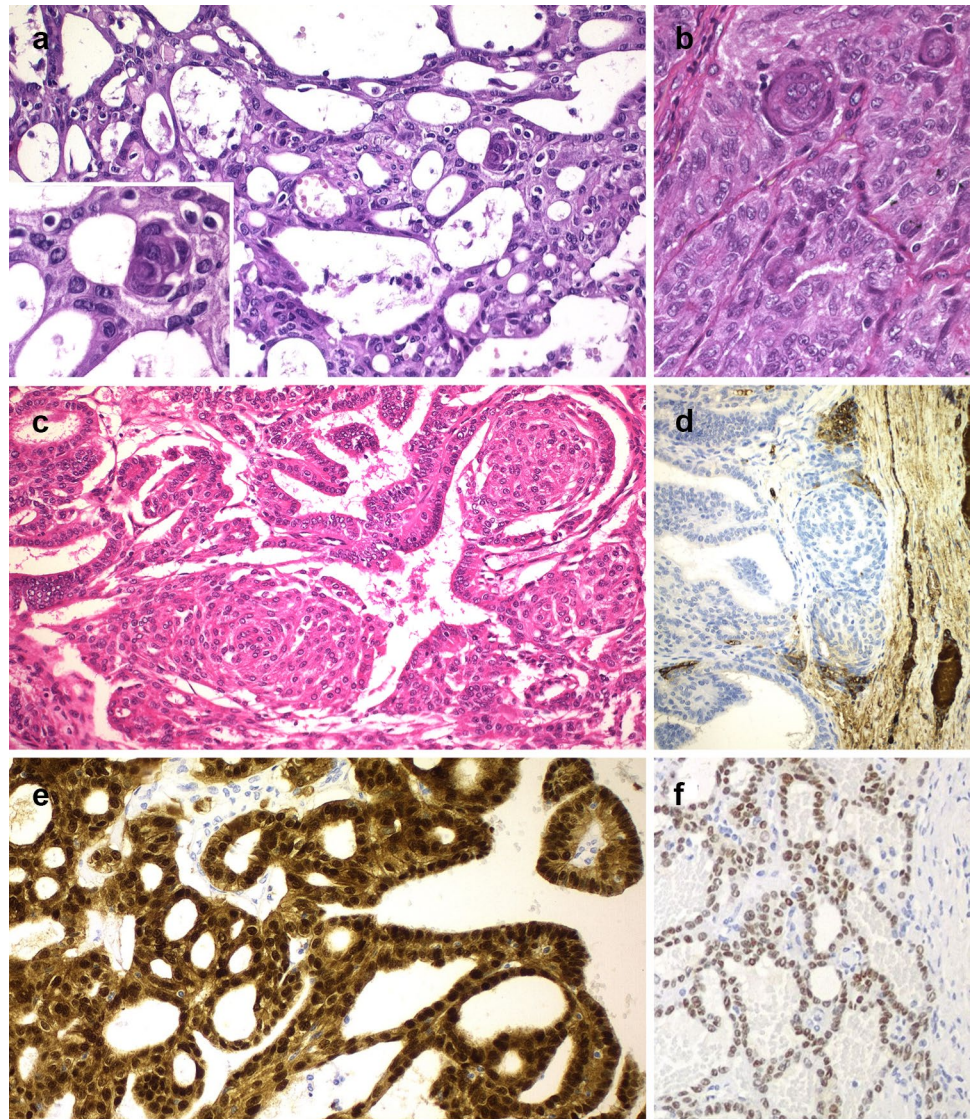
columnar with spindle cytoplasm and obscure nuclei, but typical nuclear features of PTC (grooves, pallor, and cytoplasmic inclusions) are usually seen. The presence of cribriform and/or morular areas as well as nuclear staining for β-catenin however, are the keys to the diagnosis of C-MV of TC [134, 147].

C-MV of TC generally has a good clinical course. Extrathyroidal extension, local recurrence, lymph node metastases, distant metastases, and death were reported in 4%, 4.5%, 10%, 6%, and 3% of cases taken from a review of 134 cases of C-MV of TC [134, 149]. Tumors with poor differentiation [143], neuroendocrine differentiation [150], and/or *TERT* promoter mutations [151] have been associated with a worse prognosis. High Ki-67 labeling indexes (22–70%) have been reported in cases of C-MV of TC with pulmonary metastases [152, 153], one of them having a good response to treatment with lenvatinib [153]. However, Ki-67

not associated with numerous mitoses does not seem to portend greater biological aggressiveness [154].

Genetic Features

FAP is caused by germline (constitutional) mutations in the *APC* gene (5q22.2) that result in a truncated or absent APC protein [126]. The severity of FAP changes according to the site of the germline *APC* gene mutation. In classic FAP, disease-associated germline mutations tend to be clustered in a small region designated the mutation cluster region (MCR), around codon/amino acid 1309 (codons 1286 to 1513) [132, 155]. In attenuated FAP, associated inherited mutations are located nearer the N-terminus or within the alternatively spliced section of exon 9 [128]. In more than 80% of patients with FAP and thyroid cancer, *APC* germline gene mutations occur between codons 140 and 1513 (largely

outside the MCR) [137, 138, 156, 157]. Most *APC* germline mutations associated with thyroid cancer occur in the 5′-portion of exon 15, in the same genomic area associated with CHRPE (codons 463–1387), and codon 1061 is also a hot spot for both C-MV of TC and hepatoblastoma [158]. While the risk of hepatoblastoma is greater in children younger than 3 years, the risk of developing thyroid cancer is greatest during the second and third decade of life [159]. For this reason, the fundoscopic confirmation of CHPRE could be an indicator of the familial character of a case of C-MV of TC while awaiting the result of the definitive genetic studies [129].

In normal follicular epithelial cells, APC protein forms a destruction complex with glycogen synthetase 3β (GSK3), casein kinase 1α and axin 1, sequestering β-catenin, and targeting it for degradation [160]. When the WNT pathway is activated, the destruction complex is uncoupled so the unphosphorylated β-catenin accumulates in the cytoplasm, translocates to the nucleus and activates transcription factors involved in proliferation and loss of differentiation. In multicentric thyroid tumors of FAP patients, it has been found that each tumor has a different somatic *APC* mutation (second hit), suggesting an independent development of each tumor through biallelic inactivation of the *APC* gene [157, 161]. The relationship between the morphology and the accumulation of beta-catenin in the C-MV of TC and the *APC* gene has also been confirmed in sporadic cases in which a somatic *APC* mutation in exon 15 at codon 1309 has been detected, with a dominant negative effect [162]. Two somatic (biallelic), inactivating *APC* variants have been identified in a sporadic case of C-MV of TC [163]. There are also sporadic cases of C-MV of TC associated with missense somatic mutations of exon 3 of the β-catenin gene (*CTNNB1*) without mutations or loss of heterozygosity (LOH) of the *APC* gene [164]. More recently, *AXIN1* somatic mutations (exons 1 and 7) have also been reported in a sporadic and a familial case of C-MV of TC, respectively [165, 166]. The set of these molecular alterations underscores the key role of the WNT/β-catenin signaling pathway in the development of both sporadic and familial forms of C-MV of TC.

Somatic molecular alterations typical of conventional (not hereditary) thyroid cancer such as *RET/PTC* rearrangements have been reported in some familial cases of C-MV of TC [150, 167–169]. *KRAS*, but not *HRAS* nor *NRAS* has been detected in 7.6% of these tumors, including in one sporadic case [170] and in another FAP-associated case [165]. *PIK3CA* somatic mutations (exon 9, codon 545) have been reported in 3 sporadic cases of C-MV of TC [171]. *TERT* promotor mutation has been reported in a sporadic case with aggressive behavior [151]. Rare somatic mutations in thyroid tumors such as in the *KMT2C* and *KMT2D* genes have been described in 1 and 4 cases of C-MV of TC, respectively, coexisting with the germline

mutation of the *APC* gene [138]. In this same series of patients with FAP and thyroid tumors, *BRAF*[V600E] somatic mutations have been detected in conventional PTCs but not in the cases displaying a C-MV phenotype [138]. Neither *BRAF*[V600E] mutations nor *PAX8/PPARγ* rearrangements have been described in the C-MV of TC [138, 151, 165, 170–172].

It has been proposed that the sporadic cases of C-MV of TC result from a combination of somatic mutations in phenotypically equivalent genes such as *APC*, *CTNNB1*, and/or *AXIN1* [134]. A similar possible pathogenetic mechanism has also been proposed for somatic mutations in the *KMT2D* gene. [136]. Somatic mutations in *RAS*, *PIK3CA*, *KMT2C*, and/or *BRAF*[V600E], as well as somatic *RET/PTC* rearrangements could act as a somatic "second-hit" in the development of other forms of thyroid cancers in affected individuals [9, 134, 138]. A tumor growth-promoting role has been attributed to the sex hormones due to the striking predominance of C-MV of TC in women and the strong expression of estrogen and progesterone receptors by tumor cells. [134]. Sporadic thyroid carcinomas unrelated to the pathogenesis of C-MV of TC may also occur in the thyroid of patients with FAP.

PTEN Hamartoma Tumor Syndromes (PTHS)

PTEN hamartoma tumor syndrome (PHTS) is an autosomal dominant disorder caused by inactivating germline *PTEN* gene mutations [173–176]. PHTS patients have diverse phenotypes such as *Cowden disease* (CS), *Bannayan-Riley-Ruvalcaba syndrome* (BRRS), *PTEN-related Proteus syndrome* (PS), and *Proteus-like syndromes*, but the PHTS designation should be used for all these syndromes, when a germline *PTEN* mutation is detected [173, 175, 177]. CS is a multiple hamartoma syndrome presenting in adulthood usually having macrocephaly, a high risk for benign and malignant tumors of the thyroid, breast and endometrium, multiple hamartomas and also various other lesions as well (see Table 2). BRRS (including *Bannayan-Rubalcaba-Riley syndrome*, *Bannayan-Zonana syndrome*, and *Myhre-Riley-Smith syndrome*) is a pediatric syndrome typically displaying macrocephalia, intestinal hamartomatous polyposis, lipomas, penile freckling, and the same cancer risk as CS [173, 174, 176, 177]. PS and Proteus-like syndromes are congenital disorders associated with malformations and hamartomatous tissue overgrowths, connective tissue nevi, hyperostoses and other lesions [173–176]. Most of these disorganized overgrowths of essentially mesenchymal elements have been more recently termed PTEN hamartoma of soft tissue (PHOST) [178]. In rare cases of Cowden and Cowden-like syndromes as well as in proteus syndrome, other

susceptibility genes have been reported (see below) [179–182].

The risk of TC in patients with PHTS ranges from 14 to 38% [183–187]. TC can occur at any age although it is more common in young adults (median 44 years), predominates in women and its clinical features are similar to those of sporadic TC [180, 187, 188]. Because thyroid cancer can occur in early childhood, ultrasound surveillance for all patients with pathogenic germline *PTEN* variants, regardless of their age, has been proposed [189]. Due to the fact that thyroid tumors are multifocal and there is increased risk of early progression to thyroid carcinoma, total thyroidectomy instead of lobectomy has been recommended in these patients [123, 185, 190].

Pathological Features

As appears in the first description of Cowden syndrome in 1963 [191], thyroid involvement is typically multinodular and bilateral, with no pathological differences between the thyroid findings in CS [123, 125, 187, 192] and BRRS [189, 192] (Fig. 3a). The thyroid gland in PHTS shows multifocal adenoma-to-carcinoma progression sequence. Histologically, follicular epithelial-derived thyroid carcinomas arise in the background of multiple cellular follicular adenomas (Fig. 3b) including lipoadenomas (Fig. 3d) as well as numerous cellular nodules (so-called microadenomas) [123, 125, 188, 189] (Fig. 3c, e).

Multinodular goiter due to multiple follicular adenomas appears in 43–75% of patients, sometimes including

Fig. 3 PTEN-hamartoma tumor syndrome (PHTS). In this case, thyroid involvement is typically multinodular and bilateral (**a**). Microscopically, the presence of multiple bilateral adenomatous nodules ("microadenomas") (**c**) and adenomas (**b**), including adenolipomas (**d**), is characteristic. Adipocytic infiltration and lymphocytic thyroiditis can also be seen (**f**). The loss of PTEN protein expression in thyroid nodules, whether in all nodules or in a subset of nodules with expression in endothelial cells (internal positive control), is both sensitive and specific for PHTS (**e**)
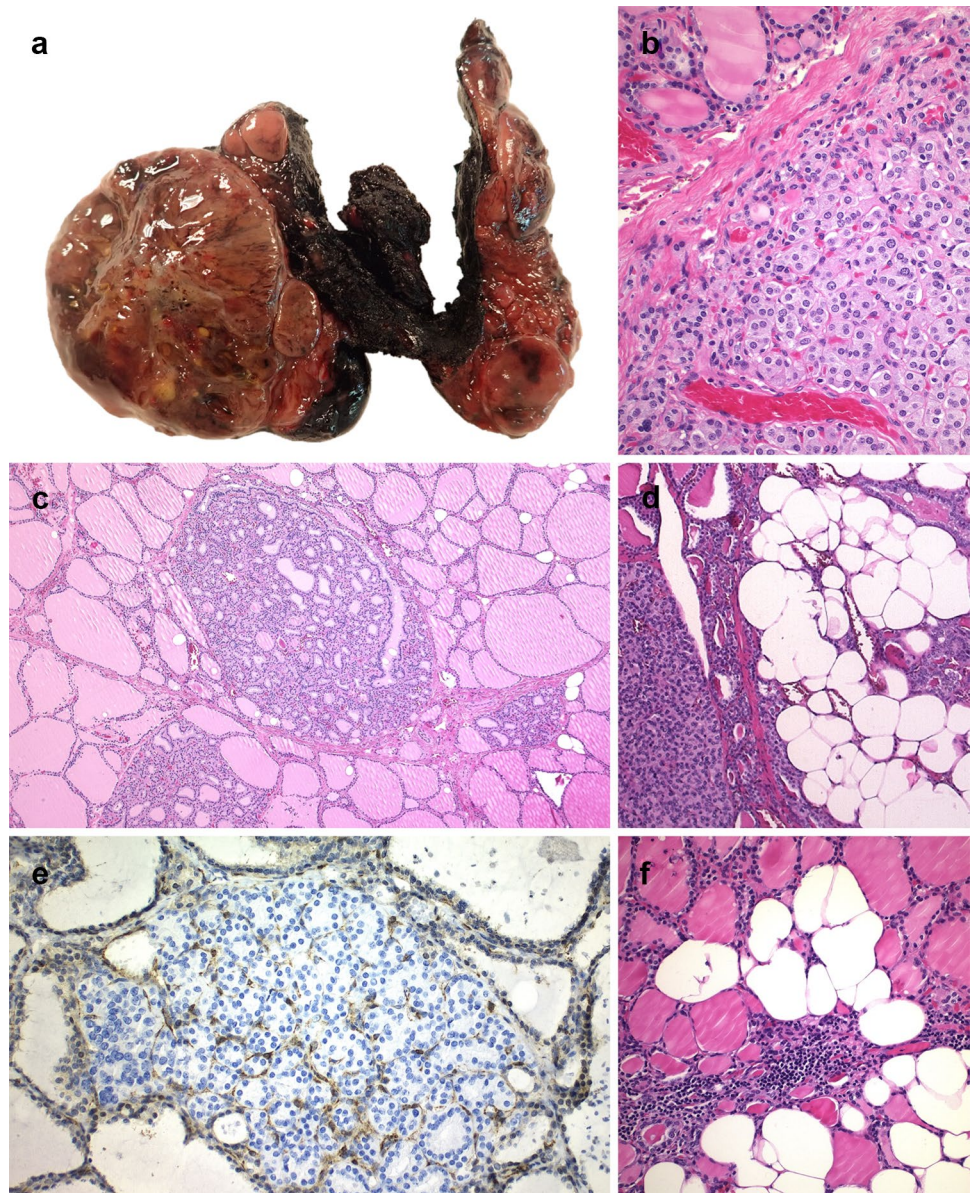
oncocytic or clear cells or a hyalinizing trabecular tumor-like pattern [123, 187, 192, 193]. The most common types of malignant tumors are PTC (60%), including the follicular variant of PTC, FTC (14–45%), poorly differentiated and anaplastic thyroid carcinoma (ATC) (6%) [123, 185, 187, 192]. Although reactive (secondary) C-cell hyperplasia has been reported in about 55% of cases [194], MTC is not a component of PHTS; scattered foci of adipose tissue distributed throughout the thyroid parenchyma as well as thyroiditis (75%) are also characteristic [116, 125, 175, 187, 192, 195] (Fig. 3f).

It is very important for pathologists to know that immunohistochemical staining of thyroidectomy specimens for PTEN protein can aid in the identification of patients with PHTS. By immunohistochemistry, the loss of PTEN protein expression in all follicular-epithelial derived thyroid nodules (including microadenomas), whether in all nodules or in a subset of nodules, is both sensitive (100%) and specific (92.3%) for CS [188]. In fact, in PHTS cases there is a loss of PTEN expression in neoplastic follicular cells, while the normal follicular cells and endothelial cells (positive control) are positive [9, 114, 125, 147, 188, 196] (Fig. 3e).

Genetic Features

PHTS is caused by pathogenic germline *PTEN* variants (10q23.31). The PTEN protein encoded by this tumor suppresor gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase that canonically counteracts the PI3K/AKT/mTOR signaling pathway [173]. Mutation or inactivation of the *PTEN* gene increases PIP3 levels causing constitutive activation of AKT with subsequent upregulation of mTOR signaling; this implies more cell proliferation, migration, angiogenesis, survival and decreased apoptosis [175, 197]. PTEN also exerts protein phosphatase-dependent and pan-phosphatase-independent actions within both the cytoplasm and the nucleus [175]. *PTEN* mutations could affect the amount of protein, causing haploinsufficiency, acting as dominant-negative, reducing or losing phosphatase activity, and/or producing abnormal localization and function [198]. In PHTS, germline mutations can affect all nine exons of the *PTEN* gene, with approximately two thirds of mutations occurring in exons 5, 7, and 8 [116, 192]. Up to 40% of all these mutations appear in exon 5, encoding the core catalytic motif [116, 175]. In addition to intragenic mutations, germline *PTEN* promoter mutations have been described in about 10% of PHTS patients [199, 200]. Furthermore, large *PTEN* deletions in about 3–10% of these patients have also been found [116, 175, 199]. Germline *PTEN* frameshift mutations have been reported to be overrepresented in TC [180], but no correlation has been found between specific germline mutations and thyroid pathological features [192].

Interestingly, in about 6% of PHTS patients, some germline variants in genes that encode subunits of mitochondrial complex II such as *SDHB*, *SDHC*, and *SDHD* (*SDHx*) can act as modifiers of PTEN-associated cancer risk and tumor histology [201]. In fact, individuals carrying the *SDHx* variants showed an increased risk of PTC, breast cancer, and renal cell cancer that exceeds the risk mediated by mutant *PTEN* alone [201]. In patients with only *PTEN* mutation, the risk of breast cancer was 32.4% and TC 25.7%, mainly FTC. With only *SDHx* variants, there was an increase in breast cancer (57.4%) and TC (51.1%) but with a predominance of PTC (including the follicular variant of PTC). But with the mutation of both *PTEN* and *SDHx* genes, the risk of breast cancer was greater (77.2%), the risk of TC decreased (27.3%), and the risk of renal cancer disappeared [201, 202].

In some studies [181], pathogenic germline *PTEN* variants have only been detected in about 25% of CS/CS-like individuals meeting the International Cowden Consortium criteria [116], and pathogenic germline *PTEN* variants have also been found in up to 11% of BRRS patients [199]. Thus, it has been postulated that in these individuals with no germline *PTEN* variants, germline mutations in other genes with a similar functional effect to those of PTEN malfunction, would explain the equivalent phenotype [202]; in fact, pathogenic germline variants in *PIK3CA* and *AKT1* [181] as well as in *EGFR* [203] genes have been reported in CS and CS-like individuals. Mutations in non-PTEN pathway genes associated with CS and BRRS that could explain the remaining patients are *SDHB*, *SDHC*, *SDHD*, *KLLN* (epimutation), *SEC23B*, *USF3*, *TTN*, *PTK2*, and *RASAL1* [179, 180, 202, 204].

A large deletion in the mitochondrial-DNA-encoded *MT-ND1* and a somatic *BRAF*^V600E mutation have been reported in a HCC and in a PTC respectively in the thyroid gland of a CS patient [205]. No *BRAF*^V600E, *NRAS* or *KRAS* somatic mutations were detected in one PTC (follicular variant), one FA, two adenolipomas and two adenomas of another patient with CS [125].

DICER1 Syndrome

DICER1 syndrome is an autosomal dominant disorder with decreased penetrance, caused by heterozygous inactivating germline *DICER1* gene mutations. *DICER1* syndrome, also designated as *Pleuropulmonary blastoma familial tumor* and *Dysplasia syndrome*, is characterized by an increased risk for pleuropulmonary blastoma, pulmonary cysts, cystic nephroma, benign and malignant thyroid tumors, Sertoli-Leydig cell tumor, gynandroblastoma, juvenile granulosa cell tumor, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, central nervous system sarcoma, and presacral malignant teratoid tumor [206–209] (see

Table 2). Additional lesions include macrocephaly, ocular and dental abnormalities, and structural alterations of the kidney and collecting system [209]. Due to its rarity, the diagnosis of pleuropulmonary blastoma, cystic nephroma or nasal chondromesenchymal hamartoma, is highly suggestive of germline *DICER1* mutation [206, 207]. Pituitary blastoma, appears to be pathognomonic of biallelic *DICER1* mutations [210, 211]. All these lesions usually occur in childhood, adolescence, or early adulthood [206–209].

An epidemiological study of individuals with one or more *DICER1*-associated lesions showed that by 20 years of age, the cumulative incidence of multinodular goiter or history of thyroidectomy is 13% in men and 32% in women, with a 16- to 24-fold increased risk of TC over a patient's lifetime [117]. Early-onset, familial, or male MNG should also alert to the possibility of *DICER1* syndrome, especially in the case of a family history of other *DICER1*-associated cancers [117, 212]. In early onset of MNG, the head circumference should also be measured, because it is also associated with *DICER1* syndrome [117], but in the absence of germline *DICER1* mutation, PHTS should also be considered (see above). For individuals with a *DICER1* pathogenic variant, thyroid ultrasound is recommended beginning at age 8 with subsequent ultrasounds every 3 to 5 years [206]. Although cases of TC reported in children had been attributed to the chemotherapy and/or radiation they had received for *DICER1*-associated tumors [213–215], germline *DICER1* mutations are associated with an increased risk of developing familial differentiated TC, even in the absence of prior treatment with chemotherapy [216]. Familial MNG and ovarian Sertoli-Leydig cell tumors [216–222] as well as co-occurrence of Sertoli-Leydig cell tumor with TC are highly suggestive of *DICER1* syndrome [223]. The diagnosis of poorly differentiated thyroid carcinoma (PDTC) in childhood or adolescence is a rare event that should also suggest the possibility of a *DICER1* syndrome [224].

Pathological Features

MNG associated with *DICER1* syndrome includes multiple and bilateral conventional follicular nodular proliferations, well-circumscribed adenomas, and/or nodules displaying intrafollicular centripedal papillary growth (so-called papillary hyperplasia or papillary adenoma) without nuclear features of papillary thyroid carcinoma [225] (Fig. 4). Most TCs are well-differentiated forms, mainly the follicular variant of PTC and minimally invasive FTC. [117]. In some cases, PTC has been described appearing within a follicular nodule [216] suggesting a stepwise progression of malignancy. Follicular cells of benign and malignant nodules (including papillary hyperplasias) sometimes show some nuclear features of PTC (intermediate-type nuclei), fitting with a carcinogenic process different from the classical pathway towards PTC or

FTC [9]; for this reason, the criteria for the diagnosis of PTC must be particularly strict in this setting. Rare cases of solid/trabecular variant of PTC [226] and PDTC (defined by the Turin consensus), have also been described in this syndrome [224]. One of the characteristics of DICER1-related thyroid disease is the high frequency of involutional change in the non-tumorous thyroid parenchyma in the absence of clinical or subclinial hyperthyroidism [225].

A rare malignant teratoid tumor of the thyroid recently designated as "thyroblastoma" [227] has been described as having somatic pathogenic *DICER1* variants but not associated with pathogenic germline *DICER1* variants [227–230] (Fig. 5). This neoplasm is characterized by a triphasic pattern combining TTF1+/PAX8+ primitive teratoid follicle-like glands admixed with neuroepithelial-like and fetal tubule-like components, with a second primitive small cell component, as well as a third cellular stroma with frequent rabdomyoblastic differentiation [227].

Genetic Features

DICER1 (14q32.13) encodes a protein possessing an RNA helicase motif containing a DEXH box in its amino terminus and an RNA motif in the carboxy terminus. The encoded protein functions as a ribonuclease and is required by the RNA interference and small temporal RNA (stRNA) pathways to produce the active small RNA component that represses gene expression. Dicer is a type III cytoplasmic endoribonuclease that is involved in the maturation of several classes of small non-coding RNAs, such as microRNAs [210, 231]. Most individuals with *DICER1* syndrome have a germline loss-of-function *DICER1* mutation with a second tumor-specific missense mutation in the RNase IIIb domain; these tumor-specific RNase IIIb missense mutations usually involve one of five hot spot codons (E1705, S1709, G1809, D1810, and E1813) [208, 210, 232]. Individuals with 14q32 deletions that encompass the *DICER1* locus are also associated with an increased risk for *DICER1*-related tumor development [233].

DICER1 mutations are rare in sporadic PTC [234]. Somatic mutations in the *DICER1* gene have been detected in two of four cases of macrofollicular variant of FTC [235]. Additional somatic RNase IIIb mutations have been detected in each of two benign follicular nodules from two patients carrying a germline *DICER1* (hot spot) mutation [225]. Another study has also found somatic *DICER1* hot spot mutations in both benign and malignant nodules from *DICER1* carriers, including different somatic *DICER1* mutations from different nodules from the same thyroid gland [117]. In a series of 40 adolescent-onset PTC cases, two somatic *DICER1* alterations were exclusively detected in each of the two PTC cases that lacked the molecular alterations typical of this tumor type (*BRAF*, *HRAS*, *KRAS*,

Fig. 4 DICER1-related thyroid disease. DICER1-related thyroidectomy specimens are grossly indistinguishable from sporadic manifestations of multinodular goiter (**a**; Lt refers to left; Rt refers to right; Sup refers to superior; Inf refers to inferior). Careful assessment of thyroid nodules and the non-lesional thyroid parenchyma provides additional clues to the possibility of DICER1-related thyroid disease. This composite photomicrograph illustrates features of thyroid pathology identified in a young adult patient with pathogenic germline *DICER1* mutation. The thyroid gland shows multifocal follicular adenomas with intrafollicular centripetal papillary projections, which are also known as papillary adenomas (**b–c**). Although papillary adenomas tend to manifest with clinical or subclinical hyperthyroidism; DICER1-related papillary adenomas are seen in association with euthyroid states. In addition, follicular-patterned thyroid neoplasms including follicular adenomas and follicular variant papillary thyroid carcinomas are identified (**c**, **f**). The nontumorous thyroid gland shows variable involutional changes characterized by dilated macro-follicles (**e**). Papillary thyroid carcinomas account for the vast majority of malignant thyroid nodules in DICER1-related thyroid disease. Encapsulated follicular variant papillary microcarcinoma with tumor capsular invasion is illustrated (**f**) along with HBME1 immunoreactivity (**g**) and reduced membranous CD56 expression (**h**)
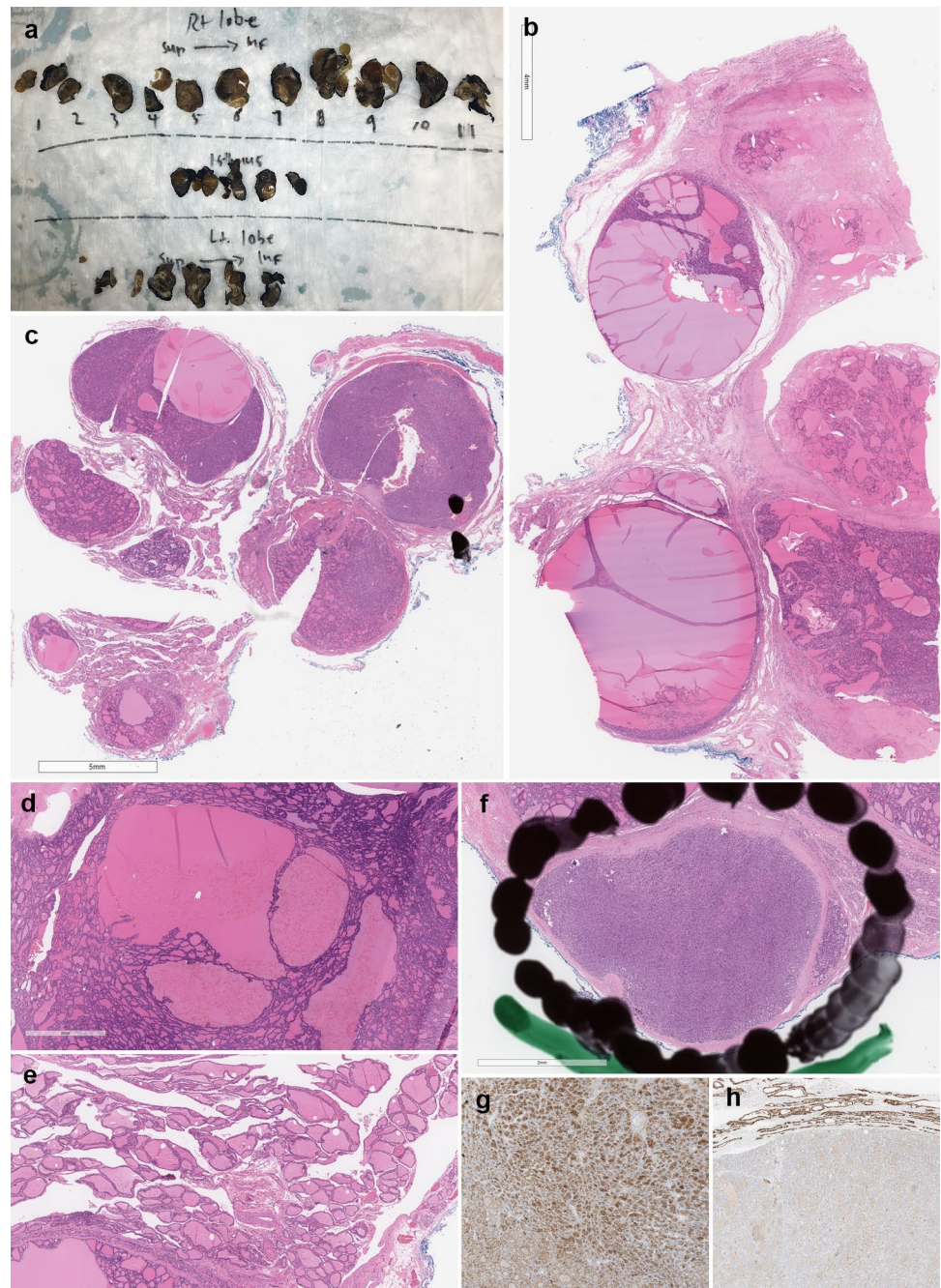

NRAS, *RET*, and *PAX8*) [225]. In a similar way, no characteristic mutations of FTC or PTC (including *TERT*) have been reported in a well-differentiated thyroid carcinoma, not otherwise specified (NOS) presenting in a young girl with MNG, botryoid rhabdomyosarcoma, and pathogenic *DICER1* mutation [236]. Childhood- and adolescent-onset PDTCs are genetically distinct from adult-onset PDTCs; they are associated with somatic *DICER1* mutations and less frequently with a germline pathogenic *DICER1* variant, but not with the classic molecular alterations

of TC [224]. All these findings support the assumption that *DICER1* syndrome-related TC may develop in a background of MNG, via a stepwise process, involving *DICER1* somatic mutations and additional molecular events, distinct from the classic pathways of TC [9, 117].

Carney Complex (CNC)

Carney complex (CNC) is an autosomal dominant disease characterized by the following major criteria for diagnosis:

Fig. 5 Thyroblastoma. In this area, the tumor is composed of a small cell undifferentiated/immature epithelial component, and a stromal chondroid component (image courtesy of Dr. Catarina Eloy, Porto, Portugal)
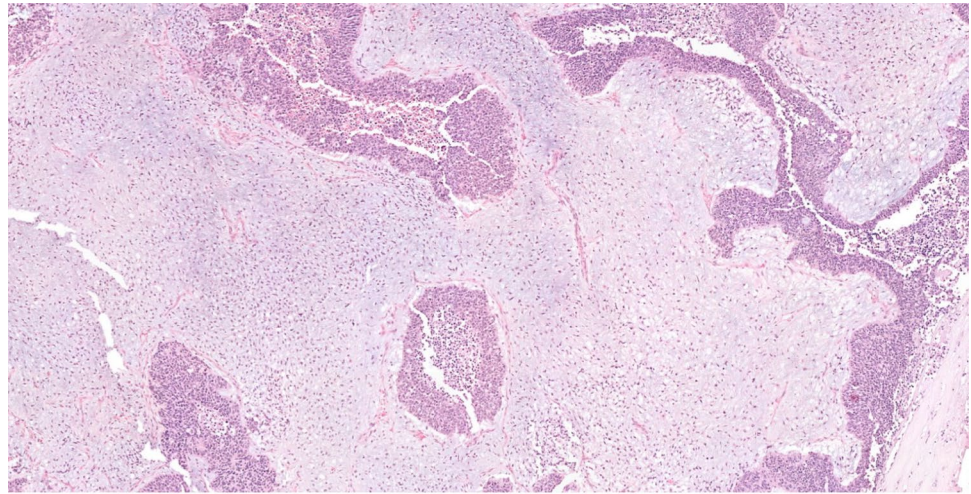
peculiar distribution of pigmentation in skin and mucosa (lips, conjunctiva and inner or outer canthi, penile, and vaginal mucosa), multiple myxomas (cutaneous, mucous, cardiac, and/or in the breast), primary pigmented nodular adrenocortical disease (Cushing syndrome), large-cell calcifying Sertoli cell tumors, acromegaly from a growth hormone (GH)-producing pituitary tumor, blue nevus, epithelioid blue nevus, breast ductal adenoma, osteochondromyxoma, and multiple thyroid nodules [237–245]. CNC has also been designated by the acronyms *NAME* (nevi, atrial myxomas, ephelides) [246] and *LAMB* (lentigines, atrial myxoma, blue nevi) [247]. It is important to recognize that the Carney triad (pulmonary chondroma, extra-adrenal paraganglioma, and gastrointestinal stromal tumor) [248, 249] is a different entity. The percentage of thyroid nodules reaches 60% among patients with CNC and 75% among children and adolescents [243, 250].

Pathological Features

The thyroid gland shows multiple and bilateral proliferative follicular lesions, including Hürthle cell nodules. There is multinodular hyperplasia, sometimes with peculiar microscopic "follicular adenomatosis" along with multiple follicular adenomas in up to 75% of CNC patients [241, 245, 251]. Follicular adenomatosis [244] is characterized by the presence of multiple encapsulated and uncapsulated follicular thyroid nodules distributed throughout the gland in a manner equivalent to the so-called microadenomas that appear in PHTS (see above). Lymphocytic thyroiditis and hyperthyroidism due to diffuse hyperplasia (Graves' disease) [252] and toxic adenoma(s) have also been reported [244]. CNC-related toxic adenomas are not different from sporadic toxic adenomas that are characterized by intrafollicular centripedal papillary growth. The term "papillary adenomas" is also applied to these functional benign neoplasms [253, 254]. The papillae in toxic adenomas contain subfollicles

and are lined by basally oriented nuclei with no features of papillary thyroid carcinomas. Although multifocal nature of these proliferations should alert the diagnostician to the possibility of a germline susceptibility, one should remember that similar findings can also occur in patients with McCune Albright syndrome, which is caused by postzygotic *GNAS* non-familial genetic mosaicism [255]. The incidence of TC is about 15% [245]. The patients usually develop well-differentiated carcinomas, both FTC and PTC, sometimes after a long history of multiple adenomas [241, 244, 256, 257]. Hürthle cell adenoma has been reported in a boy with CNC [258].

Genetic Features

In more than half of cases, CNC is caused by a heterozygous germline pathogenic variant in *PRKAR1A* gene (17q24.2) [245]. *PRKAR1A* gene encodes the regulatory subunit type I alpha of the protein kinase A (PKA, cAMP-dependent protein kinase) enzyme [250]. In a series of 353 patients with CNC, pathogenic germline *PRKAR1A* variants were detected in 73% of patients, with a penetrance close to 100%, and most mutations (82%) led to lack of detectable mutant protein because of non-sense mRNA [243]. The percentage of mutations reaches 80% in those patients with primary pigmented nodular adrenocortical disease (the so-called PPNAD) [243]. In some patients with clinical criteria of CNC without *PRKAR1A* mutation, a second locus has been identified at 2p16 [259], but for the majority of *PRKAR1A*-negative CNC cases the genetic cause is unknown [245].

Werner Syndrome (WS)

Werner Syndrome (WS) is an autosomal recessive disease with genetic instability and cancer predisposition caused by biallelic *WRN* pathogenic variants [260, 261]. WS (also called

progeria of the adult) is associated with an acceleration of biological aging and elevated risk of cancer [260]. WS is characterized by premature graying and/or thinning of scalp hair, bilateral ocular cataracts, deep, chronic ulcers around the ankles, and short stature, with symptoms typically starting in the 20s. Additional signs and symptoms include thin limbs, osteoporosis, pinched facial features, voice change, hypogonadism, type 2 diabetes mellitus, soft tissue calcification, atherosclerosis, and cancer [260, 262, 263]. In a systemativc review, the ratio male/female has been higher among Japan-resident WS patients than among patients residing outside Japan (79:58 vs. 23:26, respectively). [264]. The most common malignant neoplasms in patients with WS are thyroid tumors, melanoma, meningioma, soft-tissue sarcomas, leukemia and preleukemic disorders, and osteosarcomas [264]. TC usually appears at a younger age (mean: 34 years), and in Japanese people with WS, the overall incidence of TC is 18% [265, 266].

Pathological Features

Among the Japanese population with WS and TC, FTC (48%) was most common, followed by PTC (35%) and anaplastic thyroid carcinoma (ATC) (13%) [266]; in this setting, ATC appears in individuals at a younger age than it does in sporadic ATC, probably due to premature aging.

Genetic Features

WRN gene (8p12) encodes a multifunctional nuclear protein that is a member of the RecQ family of DNA helicases [267]. WRN protein seems to be involved in DNA repair, recombination, replication, and transcription [261]. Additionaly, WRN protein is implicated in the maintenance of telomeres [268]. In individuals of Japanese descent, PTC has been associated with the c.1105C>T, p.R369* mutation, whereas FTC was associated with the c.3139-1G>C mutation (exon 26 skip), but the mutational spectrum is different between Japanese and Caucasian patients [266]

Conclusions

Cancer derived from thyroid follicular epithelial cells is common; it represents the most common endocrine malignancy. The molecular features of the sporadic tumors have been clarified in the past decade. However the incidence of familial disease has not been emphasized and is often overlooked in routine practice. In this review, we have summarized a large body of information about both syndromic and non-syndromic familial thyroid carcinomas. In syndromic cases, the morphology of the tumor(s), molecular immunohistochemistry (e.g., PTEN, beta-catenin, SDHB),

the findings in the non-tumorous thyroid parenchyma, and other associated lesions may provide insight into the underlying disorder. However, the increasing evidence of familial predisposition to non-syndromic thyroid cancers is raising questions about the importance of genetics and epigenetics. What appears to be "sporadic" in becoming less often truly so and more often an opportunity to identify and understand novel genetic variants that underlie tumorigenesis. Pathologists must be aware of the unusual morphologic features that are harbingers of specific germline susceptibility syndromes and can assist in providing information to uncover biomarkers that will facilitate screening and early detection to prevent aggressive disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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