A unique case of two somatic APC mutations in an early onset cribriform-morular variant of papillary thyroid carcinoma and overview of the literature

M. D. Aydemirli1 · K. van der Tuin2 · F. J. Hes2 · A. M. W. van den Ouweland3 · T. van Wezel4 · E. Kapiteijn1 · H. Morreau4

Published online: 9 October 2019 © The Author(s) 2019

Abstract

We report a case of a 22-year-old female patient who was diagnosed with a cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC). While at early ages this thyroid cancer variant is highly suggestive for familial adenomatous polyposis (FAP), there was no family history of FAP. In the tumor biallelic, inactivating APC variants were identified. The patient tested negative for germline variants based on analysis of genomic DNA from peripheral blood leukocytes. Somatic mosaicism was excluded by subsequent deep sequencing of leukocyte and normal thyroid DNA using next generation sequencing (NGS). This report presents a rare sporadic case of CMV-PTC, and to the best of our knowledge the first featuring two somatic APC mutations underlying the disease, with an overview of CMV-PTC cases with detected APC and CTNNB1 pathogenic variants from the literature.

Keywords Cribriform-morular · Thyroid carcinoma · Cribriform-morular variant papillary thyroid carcinoma · APC · β-catenin · Wnt · Familial adenomatous polyposis · FAP

Introduction

The cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is a rare subtype of differentiated thyroid cancer and generally has a good prognosis [1]. CMV-PTC is highly associated with heterozygous germline APC mutations leading to familial adenomatous polyposis (FAP) [2, 3]. FAP, an autosomal dominant disorder, is characterized by multiple adenomatous colorectal polyps, often showing progression into adenocarcinoma and predisposition for a large spectrum of extracolonic tumors, including thyroid cancer. De novo APC mutations are reported in 11–25% of FAP patients [4, 5]. About 39–53% of reported CMV-PTC cases in literature were found to harbor a germline APC variant or were clinically diagnosed with FAP [6, 7]. However, CMV-PTC may also occur sporadically in the absence of FAP.

CMV-PTC has a distinctive histologic morphology featuring morules and a cribriform growth pattern, which is related to the permanent activation of the Wnt pathway, and reflected by nuclear β-catenin staining on immunohistochemistry (IHC) [1, 8]. The latter may result from biallelic APC gene inactivation, or from somatic mutations of the β-catenin (CTNNB1) [8–12] or AXIN1 gene (or combinations of gene variants), that are functionally similar [1, 13]. As the APC gene acts as a negative regulator of the Wnt pathway, mutated APC may result in a truncated protein lacking the majority of β-catenin binding sites, consequentially being unable to degrade β-catenin along with cytoplasmic and nuclear storage, while regulation of the latter is critical to the tumor suppressive effect of APC [14].
Here we present an extremely rare case of a young woman with sporadic CMV-PTC, in whom biallelic somatic inactivating APC variants were detected.

**Case description**

A 22-year-old female with an unremarkable medical history and negative family history for thyroid disease, presented with a palpable thyroid mass. Ultrasonography revealed a solitary thyroid nodule, measuring 1.5 cm by 1.8 cm by 2.1 cm, located on the right lobe, with an isoechoic and hyper-vascular composition. Cytologic findings on fine-needle aspiration (FNA) of the nodule were suggestive of PTC (Bethesda V). Total nucleic acid (undivided DNA and RNA) was isolated from FNA material using a fully automated extraction procedure [15]. No somatic DNA variants were identified upon analysis with a customized NGS AmpliSeq Cancer Hotspot Panel which includes well known thyroid carcinoma driver genes (e.g. BRAF, NRAS, HRAS, KRAS, TP53, PIK3CA and CTNNB1). A total thyroidectomy was performed with intraoperative frozen-section biopsy that was concordant with FNA findings. Histologically, the encapsulated tumor was highly cellular and composed of a combination of trabecular, solid, cribriform and follicular growth patterns with morules (Online Resource 1). Immunohistochemical (IHC) analysis for β-catenin, performed as previously described [16], showed both positively stained nuclei and cytoplasm, indicative of activation and characteristic for CMV-PTC [3].

APC was sequenced as previously described [17], on tumor DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissue cores.

Biallelic, class 4 (likely pathogenic) and class 5 (pathogenic), respectively, somatic inactivating APC variants were identified (NM_000038.5): c.3124delA, p. (Ser1042Valfs*14) and c.3183_3187delACAAA, p. (Gln1062*). The patient was referred for genetic counselling.

To explore the chances for having FAP based on these findings, the patient was referred for genetic counselling. There was no family history of any FAP related tumors, in particular, no colon cancer or colonic polyposis. Genomic DNA was extracted from peripheral blood leukocytes according to standard procedures using Sanger sequencing and multiplex ligation-probe amplification (MLPA). All 15 exons of the APC gene were negative for germline variants. Subsequent screening of DNA from leukocytes and normal thyroid tissue for the two somatic APC variants was performed using NGS deep sequencing (coverage of the variant region minimally 1000 X). The specific variants were not identified in the leukocyte DNA or normal thyroid, excluding somatic mosaicism. Therefore, referral for endoscopic surveillance, as well as genetic counselling of related family members was considered unwarranted. As standard of care, the patient received complementary ablation therapy with radioactive iodine. The patient had a total remission and also no recurrence was noted during follow up.

**Literature overview**

In Table 1 an overview of pathogenic variants in APC or CTNNB1 genes detected in 44 cases of CMV-PTC patients reported in literature is listed (Table 1). We conducted a Pubmed search on English literature using a combination of the terms: cribriform-morular, cribriform or morul* combined with thyroid carcinoma. Most of selected papers were reported in the reviews by Lam et al. [7] and/or Pradhan et al. [6] and additional relevant papers were found through cross-referencing. Reported variants in literature linked to the Catalogue of Somatic Mutations in Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cosmic) and NCBI ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or variants that could be retrieved from Leiden Open-source Variation Database (LOVD) (http://www.lovd.nl/3.0/home) were listed and annotated according to the Human Genome Variation Society (HGVS) guidelines for nomenclature (http://www.hgvs.org/content/guidelines).

Pathogenic APC variants were described in 39 cases. Of these, 36 cases had a germline APC variant including one whole gene deletion. Six of those cases with a germline APC variant were shown to harbor one additional somatic APC variant or per tumor nodule a distinct variant or LOH. One case with a germline APC variant harbored two concurrent somatic CTNNB1 variants at a different tumor site each. Three cases were reported with one somatic APC mutation solely. APC germline variants were located between codons 140 and 1309 and APC somatic variants between codons 308–1556. Only a limited number of cases were analyzed for LOH of the APC gene [9, 12, 20–22].

Six cases have been reported with somatic CTNNB1 mutations, comprising 8 different variants of CTNNB1, all of them located on exon 3. Four cases harbored single somatic CTNNB1 variants. One case harbored two somatic CTNNB1 mutations, both in different tumor nodules.

Reported mutations occurring in other than the aforementioned genes in Table 1, include two somatic mutations in exon 7 and 1 of AXIN1, that codes for a scaffold protein in the multimolecular complex that is formed by the APC protein with β-catenin and glycogen synthase kinase 3 β (GSK-3β), in a familial and a sporadic case of CMV-PTC, respectively [1, 13]. Furthermore, one apparently sporadic 45-year-old female patient case with CMV-PTC and a somatic TERT promoter mutation (c. 124C>T) showed an aggressive disease course, in absence of an APC mutation; CTNNB1 was not evaluated in this case [37]. RET/
A unique case of two somatic APC mutations in an early onset cribriform-morular variant of...

Table 1 Overview of likely pathogenic APC and CTNNB1 gene variants in CMV-PTC patient cases reported in literature

| Sex age | Germline pathogenic APC variant | Exon T | Somatic pathogenic APC variant | Exon LOH | Somatic pathogenic CTNNB1 variant | Exon | References |
|---------|--------------------------------|--------|--------------------------------|----------|----------------------------------|------|------------|
| F 23 yr | –                              | T1     | –                              | –        | c.65T>C, p.(Val22Ala)            | 3    | [9]        |
|         |                                 |        | T2                              | –        | c.166G>A, p.(Asp56Asn)           | 3    |            |
| F 20 yr | –                              |        | –                              | ND       | c.110C>T, p.(Ser37Phe)           | 3    | [8]        |
| F 34 yr | –                              |        | –                              | –        | c.85T>C, p.(Ser29Pro)            | 3    | [9]        |
| F 22 yr | –                              |        | –                              | –        | c.160G>A, p.(Glu54Lys)           | 3    | [9]        |
| F 23 yr | ND                             |        | ND                             | ND       | c.115G>A, p.(Ala39Thr)           | 3    | [9]        |
| F 30 yr | c.1538delT, p.(Val513Glufs*10)  | 11     | T1                              | –        | c.145A>G, p.(Lys49Glu)           | 3    | [9, 18]    |
|         |                                 |        | T2                              | –        | c.131C>T, p.(Pro44Leu)           | 3    |            |
| F 29 yr | Whole gene deletion            |        | c.1548+1G>A, splice site variant | e        | +                                | ND   | [19]       |
| F 25 yr | c.1660C>T, p.(Arg554*)         | 13     | T1                              | c.922delC, p.(Leu308fs*28) | 8    | –        | –        | [20] |
|         |                                 |        | T2                              | c.2706_2725del20, p.(Glu902fs*3) | 15 | –        | –        |
|         |                                 |        | T3                              | c.1821delT, p.(Cys607fs*3) | 14 | –        | –        |
|         |                                 |        | T4                              | c.1920delG, p.(Asn641fs*5) | 14 | –        | –        |
|         |                                 |        | T5                              | c.2803_2804insA, p.(Tyr955fs*1) | 15 | –        | –        |
|         |                                 |        | T6                              | c.1602delA, p.(Lys534fs*15) | 12 | –        | –        |
| F 20 yr | c.3329C>G, p.(Ser1110*)        | 15     | T1                              | c.3180_3184delAAAAC, p.(Gln1062fs*1) | 15 | ND       | ND       | [21, 22] |
|         |                                 |        | T2                              | c.2569G>T, p.(Gly857*) | 15 | ND       | ND       |
| F 26 yr | c.524delC, p.(Thy175Metfs*10)  | 4      | T1                              | c.2656C>T, p.(Gln886*) | 15 | –        | ND       | [21, 22] |
|         |                                 |        | T2                              | c.4606G>T, p.(Glu1536*) | 15 | –        | ND       |
|         |                                 |        | T3                              | c.4666_4667insA, p.(Thr1556fs*3) | 15 | –        | ND       |
|         |                                 |        | T4                              | –        | +                                | ND   |            |
|         |                                 |        | T5                              | –        | +                                | ND   |            |
| F 24 yr | c.2093T>G, p.(Leu698*)         | 15     | T1                              | c.4362_4567ins159, p.(Lys1454fs*3) | 15 | ND       | ND       | [11] |
| F 21 yr | c.832C>T, p.(Gln278*)          | 7      | T1                              | c.1363_1378delinsTTTCTC, p.(Lys455Phefs*9) | 10 | ND       | ND       | [23] |
| F 48 yr | c.832C>T, p.(Gln278*)          | 7      | –                              | –        | ND                               | ND   | [23] |
| M 42 yr | Duplication                    | 2/3    |                                 | –        | ND                               | –    | [12]       |
| F 27 yr | c.1917insA, p.(Arg640Thrfs*11) | 14     |                                 | ND       | ND                               | ND   | [24]       |
| F 40 yr | c.3149delC, p.(Ala1050Glufs*6) | 15     |                                 | ND       | ND                               | ND   | [24]       |
| Sex | Age | APC variant | Exon | T | APC variant | Exon | LOH | CTNNB1 variant | Exon | References |
|-----|-----|-------------|------|---|-------------|------|-----|----------------|------|------------|
| F   | 32 yr | 'abnormal splicing in exon 9'; molecular defect not identified | 9 | ND | ND | ND | ND | [18, 25] |
| F   | 29 yr | c.3927_3931del, p.(Glu1309Aspfs*4) | 15 | ND | ND | ND | ND | [26] |
| F   | 30 yr | c.419_422del, p.(Glu140Glyfs*28) | 3 | – | ND | ND | [27] |
| F   | 19 yr | c.1775T>G, p.(Leu592*) | 14 | – | ND | ND | ND | [27] |
| F   | 22 yr | c.2336del p.(Leu779*) | 15 | – | ND | ND | [27] |
| F   | 18 yr | c.2928_2929del, p.(Gly977Serfs*7) | 15 | – | ND | ND | [27] |
| F   | 27 yr | c.2979del, p.(Lys993Asnfs*12) | 15 | – | ND | ND | ND | [27] |
| F   | 39 yr | c.3183_3187del, p.(Gln1062*) | 15 | – | ND | ND | ND | [27] |
| F   | 26 yr | c.3927_3931del, p.(Glu1309Aspfs*4) | 15 | – | ND | ND | ND | [27] |
| F   | 22 yr | c.3183_3187del, p.(Gln1062*) | 15 | – | ND | ND | ND | [27] |
| F   | 20 yr | c.3183_3187del, p.(Gln1062*) | 15 | – | ND | ND | ND | [27] |
| F   | 36 yr | c.3183_3187del, p.(Gln1062*) | 15 | – | ND | ND | ND | [27] |
| F   | 24 yr | c.3183_3187del, p.(Gln1062*) | 15 | – | ND | ND | ND | [27] |
| F   | 20 yr | c.3927_3931del, p.(Glu1309Aspfs*4) | 15 | – | ND | ND | ND | [27] |
| F   | 27 yr | c.3927_3931del, p.(Glu1309Aspfs*4) | 15 | – | ND | ND | ND | [27] |
| F   | 20 yr | c.3183_3187del, p.(Gln1062*) | 15 | ND | ND | ND | ND | [28] |
| F   | 38 yr | c.2093T>A, p.(Leu698*) | 15 | – | ND | ND | ND | [11] |
| F   | 49 yr | c.937_938delGA, p.(Glu313Asnfs*) | 9 | – | ND | ND | ND | [11] |
| F   | 16 yr | c.254A>T, p.(Lys848*) | 15 | ND | ND | ND | ND | [29, 30] |
| F   | 12 yr | c.254A>T, p.(Lys848*) | 15 | ND | ND | ND | ND | [29, 30] |
| F   | 18 yr | c.3183_3187del, p.(Gln1062*) | 15 | ND | ND | ND | ND | [31] |
| F   | 30 yr | c.3317delG, p.(Gly1106Glufs*20) | 15 | ND | ND | ND | ND | [32] |
| F   | 21 yr | c.2211C>G, p.(Tyr737*) | 15 | ND | ND | ND | ND | [33] |
| F   | 40 yr | Unknown variant in codon 1219 | 15 | – | ND | ND | ND | [27] |
| F   | 19 yr | Unknown variant in codon 1219 | 15 | – | ND | ND | ND | [27] |
| F   | 35 yr | – | 12 | ND | – | [34] |
| F   | 19 yr | – | 15 | ND | ND | [35] |
PTC rearrangements have also been reported in sporadic CMV-PTC [38], and in FAP associated cases [11, 12]. High rates of RET/PTC gene activation have been reported by Cetta et al. [39] in cases with heterozygous APC genes, although somatic mutations were not determined [22], with hypotheses of a tissue-specific dominant effect [40]. Somatic PIK3CA c.1634 A>C (p.E545A) mutations were reported in three sporadic CMV-PTC cases of female patients aged 14, 16, 17 years [41], and suggested as a potential candidate gene involved in sporadic CMV-PTC tumorigenesis in absence of a CTNNB1 mutation, however, APC gene mutation data are lacking. A 16-year old female FAP patient was reported with a somatic KRAS mutation (c. 181C>A (p. Q61K)); however, data on APC (or CTNNB1) genes were not reported [42].

**Discussion**

In the present report we describe a young adult patient with cribriform-morular variant of PTC with biallelic somatic inactivating APC variants. To the best of our knowledge, it represents the first case of two pathogenic somatic APC variants explaining the disease occurrence.

The class 5 APC variant c.3183_3187delACAAA, p. (Gln1062*), has previously been described as a germline pathogenic variant in a FAP patient with PTC [43]. The other APC variant c.3124delA, p. (Ser1042Valfs*14) was not reported before, but was considered a class 4 (likely pathogenic) variant. The pathogenicity of variants is annotated in classes 1 to 5, with a class 4 variant being likely pathogenic and a class 5 variant being (well-known) pathogenic [44], based on literature (Pubmed) search and common or locus specific databases (Mycancergenome, Alamut Visual, NCBI dbSNP, NCBI ClinVar, COSMIC, Jackson laboratory database, LOVD, MD Anderson database).

Also, the finding of a solitary nodule in our patient, is in line with its usual appearance in sporadic cases [1].

The detection of the biallelic inactivating mutations is in line with the Knudson “two-hit hypothesis” [45], supporting the underlying nature for the tumor.

Germline variants in APC are frequently found in FAP patients, but absent in the CTNNB1 gene [46, 47]. The occurrence of a germline CTNNB1 variant has only been reported as an inactivating mutation, constituting another distinct phenotype without tumor manifestations, in two siblings, of whom the parents most likely harbored germline mosaicism [48]. Cetta et al. reported that biallelic inactivation of APC is usually lacking in thyroid carcinoma cases occurring in FAP [49]. The latter might be suggestive of a conveyance of a general susceptibility to thyroid tumorigenesis [50]. On the other hand, this could also be partly due to a limited or a lack of mutational analysis of the APC and/or CTNNB1 gene (indicated as ND, not determined, in Table 1).

The CTNNB1 variants in the cases listed in the overview (Table 1) were all located on exon 3, which is typically associated with β-catenin translocation from membrane to nucleus and Wnt pathway activation [51].

The majority of the reported somatic and germline APC variants in CMV-PTC (Table 1, [27]), were not within the mutation cluster region (MCR) in APC (codons 1286–1513) for somatic mutations in colorectal tumors [52]. Of the reported 17 somatic APC variants, 3 variants occurred in, 12 before and 2 after the MCR, respectively (Table 1). Of the reported 36 germline APC variants, 4 occurred in and 31 before the MCR (one of the germline variants was a whole gene deletion) (Table 1).
However, all germline APC variants (Table 1) were within the region extending from codons 140 to 1309, that has been associated to PTC in terms of genotype-phenotype correlations of extra-intestinal manifestations of FAP [39, 53, 54]. Of the 17 reported somatic APC variants (Table 1), 3 variants were out of and 14 variants were in this region (codons 140–1309), as well as the two somatic APC variants identified in the index patient.

In conclusion, in the current study, we report biallelic somatic (rather than germline) pathogenic APC variants in a young female CMV-PTC patient. Our report corroborates current ideas regarding the molecular background in CMV-PTC tumors. The true somatic nature of the variants found, was rendered most likely, using deep APC sequencing of leukocyte and normal DNA to exclude mosaicism. Accordingly, endoscopy was not performed. With a substantial share of FAP patients having a de novo APC mutation [4, 5], the presently reported approach conveys added value and clinical relevance especially in patients with an absent family history of FAP. As much so in patients without any evidence of detected FAP as of yet, with about 60% of total CMV-PTC being FAP associated, of whom a substantial proportion is preceded by that of thyroid cancer [1].

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required. Patient samples were handled according to medical ethical guidelines as described in the Code for Proper Secondary Use of Human Tissue established by the Dutch Federation of Medical Sciences (www.feder a.org; accessed January 2019). The patient has made no objections against the use of the anonymized patient data in this report.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Cameselle-Teijeiro JM et al (2018) Cribriform-morular variant of thyroid carcinoma: a neoplasm with distinctive phenotype associated with the activation of the WNT/beta-catenin pathway. Mod Pathol 31(8):1168–1179
2. Steinhagen E et al (2012) The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. Clin Colorectal Cancer 11(4):304–308
3. Nose V (2011) Familial thyroid cancer: a review. Mod Pathol 24(Suppl 2):S19–S33
4. Bjork J et al (1999) Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. Scand J Gastroenterol 34(12):1230–1235
5. Bisgaard ML et al (1994) Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 3(2):121–125
6. Pradhan D, Sharma A, Mohanty SK (2015) Cribriform-morular variant of papillary thyroid carcinoma. Pathol Res Pract 211(10):712–716
7. Lam AK, Saremi N (2017) Cribriform-morular variant of papillary thyroid carcinoma: a distinctive type of thyroid cancer. Endocr Relat Cancer 24(4):R109–R121
8. Jung CK et al (2009) The cytological, clinical, and pathological features of the cribriform-morular variant of papillary thyroid carcinoma and mutation analysis of CTNNB1 and BRAF genes. Thyroid 19(8):905–913
9. Xu B et al (2003) Cribriform-morular variant of papillary thyroid carcinoma: a pathological and molecular genetic study with evidence of frequent somatic mutations in exon 3 of the beta-catenin gene. J Pathol 199(1):58–67
10. Cetta F et al (1999) Genetics and clinicopathological findings in thyroid carcinomas associated with familial adenomatous polyposis. Am J Pathol 155(1):7–9
11. Soravia C et al (1999) Familial adenomatous polyposis-associated thyroid cancer: a clinical, pathological, and molecular genetics study. Am J Pathol 154(1):127–135
12. Cameselle-Teijeiro J et al (2009) Cribriform-morular variant of papillary thyroid carcinoma: molecular characterization of a case with neuroendocrine differentiation and aggressive behavior. Am J Clin Pathol 131(1):134–142
13. Cameselle Teijeiro JPG, Carreira D, Abdulkader M, Reyes-Santías I, Celestino R, Romero Rojas R, Ruiz Ponte A, Soares C, Casanueva P, Sobrinho F, Simões M (2016) Molecular alterations in the cribriform-morular variant of papillary thyroid carcinoma. Virchows Arch 469(1 Supplement):S72
14. Morin PJ (1999) Beta-catenin signaling and cancer. Bioessays 21(12):1021–1030
15. van Eijk R et al (2013) Assessment of a fully automated high-throughput DNA extraction method from formalin-fixed, paraffin-embedded tissue for KRAS, and BRAF somatic mutation analysis. Exp Mol Pathol 94(1):121–125
16. Hermsen IG et al (2013) Mutational analyses of epidermal growth factor receptor and downstream pathways in adrenocortical carcinoma. Eur J Endocrinol 169(1):51–58
17. Jansen AM et al (2017) Distinct patterns of somatic mosaicism in the APC gene in neoplasms from patients with unexplained adenomatous polyposis. Gastroenterology 152(3):546–549.e3
18. Tomoda C et al (2004) Cribriform-morular variant of papillary thyroid carcinoma: clue to early detection of familial adenomatous polyposis-associated colon cancer. World J Surg 28(9):886–889
19. Coren J et al (2018) Cribriform-morular variant of papillary thyroid carcinoma with poorly differentiated features: a case report with immunohistochemical and molecular genetic analysis. Int J Surg Pathol 27(3):294–304
20. Uchino S et al (2006) Mutational analysis of the APC gene in cribriform-morular variant of papillary thyroid carcinoma. World J Surg 30(5):775–779
21. Miyaki M et al (2000) Cribriform-morular variant of papillary thyroid carcinoma: a neoplasm with distinctive phenotype associated with the activation of the WNT/beta-catenin pathway. Mod Pathol 13(2):121–125
22. Hirasawa K et al (2000) Cribriform-morular variant of papillary thyroid carcinoma. Clin Exp Med Sci (Tokyo) 46(2):159–162
A unique case of two somatic APC mutations in an early onset cribriform-morular variant of papillary thyroid carcinoma. Jpn J Cancer Res 90(4):372–376

23. Kameyama K et al (2004) Cribriform-morular variant of papillary thyroid carcinoma: ultrastructural study and somatic/germline mutation analysis of the APC gene. Ultrastruct Pathol 28(2):97–102

24. Casellas-Cabrera N et al (2016) Risk of thyroid cancer among Caribbean Hispanic patients with familial adenomatous polyposis. Fam Cancer 15(2):267–274

25. Xu B et al (2003) A predominant increase in the APC gene isoform with exon 9a in a case of attenuated familial adenomatous polyposis. Clin Genet 63(1):71–72

26. Lee S et al (2004) Papillary thyroid carcinoma associated with familial adenomatous polyposis: molecular analysis of pathogenesis in a family and review of the literature. Endocr J 51(3):317–323

27. Cetta F et al (2000) Germline mutations of the APC gene in patients with familial adenomatous polyposis-associated thyroid carcinoma: results from a European cooperative study. J Clin Endocrinol Metab 85(1):286–292

28. Fenton PA et al (2001) Cribriform variant papillary thyroid cancer: a characteristic of familial adenomatous polyposis. Thyroid 11(2):193–197

29. Chong J et al (2000) Aspiration and imprint cytopathology of thyroid carcinoma associated with familial adenomatous polyposis. Diagn Cytopathol 23(2):101–105

30. Kashiwagi H et al (1996) Sisters with familial adenomatous polyposis affected with thyroid carcinoma, desmoid tumour and duodenal polyposis. Br J Surg 83(2):228

31. Paraf F et al (1997) [Familial adenomatous polyposis and thyroid cancer]. Gastroenterol Clin Biol 21(1):74–77

32. Miyaki M et al (1993) Coexistence of somatic and germ-line mutations of APC gene in desmoid tumors from patients with familial adenomatous polyposis. Cancer Res 53(21):5079–5082

33. Akaishi J et al (2018) Cribriform-morular variant of papillary thyroid carcinoma: clinical and pathological features of 30 cases. World J Surg 42(11):3616–3623

34. Nakazawa T et al (2013) Cribriform-morular variant of papillary thyroid carcinoma displaying poorly differentiated features. Int J Surg Pathol 21(4):379–389

35. Subramaniam MM et al (2007) Clonal characterization of sporadic cribriform-morular variant of papillary thyroid carcinoma by laser microdissection-based APC mutation analysis. Am J Clin Pathol 128(6):994–1001

36. Cameselle-Teijeiro J et al (2001) Somatic but not germline mutation of the APC gene in a case of cribriform-morular variant of papillary thyroid carcinoma. Am J Clin Pathol 115(4):486–493

37. Oh EJ et al (2017) TERT promoter mutation in an aggressive cribriform-morular variant of papillary thyroid carcinoma. Endocr Pathol 28(1):49–53

38. Brehar AC et al (2016) Cribriform-morular variant of papillary thyroid carcinoma at pediatric age—case report and review of the literature. Rom J Morphol Embryol 57(2):531–537

39. Cetta F et al (1998) Genetic alterations in thyroid carcinoma associated with familial adenomatous polyposis: clinical implications and suggestions for early detection. World J Surg 22(12):1231–1236

40. Cetta F (1999) Comment on Carney complex and related syndromes and their genetic loci. J Clin Endocrinol Metab 84(4):1491–1492

41. Kwon MJ et al (2015) Cribriform-morular variant of papillary thyroid carcinoma: a study of 3 cases featuring the PIK3CA mutation. Hum Pathol 46(8):1180–1188

42. Giannelli SM et al (2014) Familial adenomatous polyposis-associated, cribriform morular variant of papillary thyroid carcinoma harboring a K-RAS mutation: case presentation and review of molecular mechanisms. Thyroid 24(7):1184–1189

43. Kim DW et al (2005) Mutation spectrum of the APC gene in 83 Korean FAP families. Hum Mutat 26(3):281

44. Den Dunnen et al (2016) HGVs recommendations for the description of sequence variants—2016 update. Hum Mutat 37:564–569

45. Knudson AG Jr (1985) Hereditary cancer, oncogenes, and antioncogenes. Cancer Res 45(4):1437–1443

46. Cao X et al (1999) Germine mutations are frequent in the APC gene but absent in the beta-catenin gene in familial adenomatous polyposis patients. Genes Chromosom Cancer 25(4):396–398

47. Dobbie Z, Muller H (1999) Germline mutations in the beta-catenin gene are not associated with the FAP phenotype without an APC mutation. J Med Genet 36(7):573–574

48. Kuechler A et al (2015) De novo mutations in beta-catenin (CTNNB1) appear to be a frequent cause of intellectual disability: expanding the mutational and clinical spectrum. Hum Genet 134(1):97–109

49. Cetta F et al (2001) Thyroid carcinoma usually occurs in patients with familial adenomatous polyposis in the absence of biallelic inactivation of the adenomatous polyposis coli gene. J Clin Endocrinol Metab 86(1):427–432

50. Cetta F (2015) FAP associated papillary thyroid carcinoma: a peculiar subtype of familial nonmedullary thyroid cancer. Patholog Res Int 2015:309348

51. Kim G et al (2018) Nuclear beta-catenin localization and mutation of the CTNNB1 gene: a context-dependent association. Mod Pathol 31(10):1553–1559

52. Miyoshi Y et al (1992) Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum Mol Genet 1(4):229–233

53. Groen EJ et al (2008) Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 15(9):2439–2450

54. Chenbhanich J et al (2019) Prevalence of thyroid diseases in familial adenomatous polyposis patients. Genes Chromosom Cancer 11(2):193–197

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.