



**Universiteit
Leiden**
The Netherlands

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

Aydemirli, M.D.; Tuin, K. van der; Hes, F.J.; Ouweland, A.M.W. van den; Wezel, T. van; Kapiteijn, E.; Morreau, H.

Citation

Aydemirli, M. D., Tuin, K. van der, Hes, F. J., Ouweland, A. M. W. van den, Wezel, T. van, Kapiteijn, E., & Morreau, H. (2020). A unique case of two somatic APC mutations in an early onset cribriform-morular variant of papillary thyroid carcinoma and overview of the literature. *Familial Cancer*, 19(1), 15-21. doi:10.1007/s10689-019-00146-4

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3184339>

Note: To cite this publication please use the final published version (if applicable).



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].

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10689-019-00146-4>) contains supplementary material, which is available to authorized users.

✉ M. D. Aydemirli
M.D.Aydemirli@lumc.nl

¹ Department of Medical Oncology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

² Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

³ Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands

⁴ Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

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*) (Online Resource 2).

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 tested 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 $\times$). 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 *AXINI*, 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-3 β), 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*/

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

Sex age	Germline pathogenic <i>APC</i> variant	Exon	T	Somatic pathogenic <i>APC</i> variant	Exon	LOH	Somatic pathogenic <i>CTNNB1</i> 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.(Val513Glu fs*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 ^d	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.(Tyr935fs*1)	15	–	–		
			T6	c.1602delA, p.(Lys534fs*15)	12	–	–		
F 20 yr	c.3329C>G, p.(Ser1110*)	15	T1	c.3180_3184delAAAAAC, p.(Gln1062fs*1)	15	ND	ND		[21, 22]
			T2	c.2569G>T, p.(Gly857*)	15	ND	ND		
F 26 yr	c.524delC, p.(Thy175Met fs*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		c.4362_4567ins159, p.(Lys1454fs*3)	15	ND	ND		[11]
F 21 yr ^a	c.832C>T, p.(Gln278*)	7		c.1363_1378delinsTTT CTC, p.(Lys455Phe fs*9)	10	ND	ND		[23]
F 48 yr ^a	c.832C>T, p.(Gln278*)	7		–		ND	ND		[23]
M 42 yr	Duplication	2/3		–		ND	–		[12]
F 27 yr	c.1917insA, p.(Arg640Thr fs*11)	14		ND		ND	ND		[24]
F 40 yr	c.3149delC, p.(Ala1050Glu fs*6)	15		ND		ND	ND		[24]

Table 1 (continued)

Sex age	Germline pathogenic <i>APC</i> variant	Exon T	Somatic pathogenic <i>APC</i> variant	Exon LOH	Somatic pathogenic <i>CTNNB1</i> variant	Exon	References
F 32 yr	'abnormal splicing in exon 9'; molecular defect not identified	9	ND	ND	ND		[18, 25]
F 29 yr	c.3927_3931del, p.(Glu1309Aspfs*4)	15	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		[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		[27]
F 39 yr	c.3183_3187del, p.(Gln1062*)	15	—	ND	ND		[27]
F 26 yr	c.3927_3931del, p.(Glu1309Aspfs*4)	15	—	ND	ND		[27]
F 22 yr ^b	c.3183_3187del, p.(Gln1062*)	15	—	ND	ND		[27]
F 20 yr ^b	c.3183_3187del, p.(Gln1062*)	15	—	ND	ND		[27]
F 36 yr ^b	c.3183_3187del, p.(Gln1062*)	15	—	ND	ND		[27]
F 24 yr	c.3183_3187del, p.(Gln1062*)	15	—	ND	ND		[27]
F 20 yr	c.3927_3931del, p.(Glu1309Aspfs*4)	15	—	ND	ND		[27]
F 27 yr	c.3927_3931del, p.(Glu1309Aspfs*4)	15	—	ND	ND		[27]
F 20 yr	c.3183_3187del, p.(Gln1062*)	15	ND	ND	ND		[28]
F 38 yr	c.2093T>A, p.(Leu698*)	15	—	ND	ND		[11]
F 49 yr	c.937_938delGA, p.(Glu313Asnfs*)	9	—	ND	ND		[11]
F 16 yr ^c	c.254A>T, p.(Lys848*)	15	ND	ND	ND		[29, 30]
F 12 yr ^c	c.254A>T, p.(Lys848*)	15	ND	ND	ND		[29, 30]
F 18 yr	c.3183_3187del, p.(Gln1062*)	15	ND	ND	ND		[31]
F 30 yr	c.3317delG, p.(Gly1106Gluufs*20)	15	ND	ND	ND		[32]
F	c.2211C>G, p.(Tyr737*)	15		ND	ND		[33]
F 40 yr	Unknown variant in codon 1219	15	—	ND	ND		[27]
F 19 yr	Unknown variant in codon 1219	15	—	ND	ND		[27]
F 35 yr	—		c.1559_1563delGCTCT, p.(Cys520fs*15)	12	ND	—	[34]
F 19 yr	—		c.3927_3931delAAAGA, p.(Glu1309fs*4)	15	ND	ND	[35]

Table 1 (continued)

Sex age	Germline pathogenic <i>APC</i> variant	Exon T	Somatic pathogenic <i>APC</i> variant	Exon	LOH	Somatic pathogenic <i>CTNNB1</i> variant	Exon	References
F 27 yr	–		c.3927_3931delAAAGA, p.(Glu1309fs*4)	15	ND	ND		[36]

References are listed in the appendix. Data in the table are ordered according to somatic *CTNNB1* mutations, then the germline *APC* variants (either coinciding with somatic mutations or without other mutations) and somatic *APC* mutations reported in literature. Within the list, a reverse chronological order has been pursued with annotation of the variants according to HGVS guidelines. The majority of somatic variants were found in the COSMIC database. Printed underlined: Germline variants found in ClinVar. The remaining variants were found in LOVD. Variants reported were curated and annotated using the *APC* reference sequence NM_000038.5

– No variants detected, *bp* base pair, *del* deletion, *F* female, *M* male, *ND* not determined, *T1*, *T2*, etc. number of tumor foci, *yr* years old

^aRelated cases (mother, daughter) belonging to the same kindred

^{b,c}Related cases (sisters) belonging to the same kindred, respectively

^dSomatic variants not found in COSMIC database

^e1 base pair downstream of exon 12

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.federatie.nl; 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. Hermesen 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. Corean 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-morula variant of papillary thyroid carcinoma. *World J Surg* 30(5):775–779
21. Miyaki M et al (2000) Molecular evidence for multicentric development of thyroid carcinomas in patients with familial adenomatous polyposis. *Am J Pathol* 157(6):1825–1827

22. Iwama T et al (1999) Somatic mutation of the APC gene in thyroid carcinoma associated with familial adenomatous polyposis. *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) Germline 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: a systematic review and meta-analysis. *Fam Cancer* 18(1):53–62

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