Brief Report

Analysis of germline variants in pediatric patients diagnosed with desmoid tumors and nuchal-type fibromas

Piedad Alba-Pavón[1]^, Itziar Astigarraga[1,2,3], Lide Alaña[1], Isabel Llano-Rivas[4], Blanca Gener[4], Lorena Mosteiro[5], Ricardo López-Almaraz[1,2], Aizpea Echebarria-Barona[1,2], Olatz Villate[1]^

[1]Pediatric Oncology Group, Biobizkaia Health Research Institute, Barakaldo, Spain; [2]Pediatrics Department, Hospital Universitario Cruces, Osakidetza, Barakaldo, Spain; [3]Pediatric Department, Universidad del País Vasco UPV/EHU, Leioa, Spain; [4]Department of Genetics, Cruces University Hospital, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain; [5]Department of Pathology, Hospital Universitario Cruces, Osakidetza, Barakaldo, Spain

Correspondence to: Olatz Villate, PhD. Pediatric Oncology Group, Biobizkaia Health Research Institute, Plaza Cruces S/N 48903, Barakaldo, Spain. Email: olatz.villatebejarano@osakidetza.eus.

Abstract: Desmoid tumor (DT) is a fibroblastic proliferation arising in soft tissue characterized by localized infiltrative growth with an inability to metastasize but with a tendency to recurrence. Nuchal-type fibromas are benign soft tissue lesions that are usually developed in the posterior neck. The development of these neoplasms can be associated with a hereditary cancer predisposition syndrome, mainly familial adenomatous polyposis (FAP) syndrome caused by *APC* germline mutations. Gardner syndrome is a variant of FAP characterized by the presence of extracolonic manifestations including soft tissue tumors as DTs and nuchal-type fibromas. However, the development of these tumors could be associated with germline alterations in other genes related to colorectal cancer development. The objective of this study was to analyze germline variants in *APC*, *MUTYH*, *POLD1* and *POLE* genes in five pediatric patients diagnosed with DTs or nuchal-type fibromas. We identified two pathogenic variants in the *APC* gene in two different patients diagnosed with nuchal-type fibroma and DTs and two variants of uncertain significance in *POLD1* in two patients diagnosed with nuchal-type fibroma. Two patients had family history of colorectal cancer, however, only one of them showed an *APC* germline pathogenic variant. The analysis of germline variants and genetic counseling is essential for pediatric patients diagnosed with DTs or nuchal-type fibromas and their relatives.

Keywords: Desmoid tumor (DT); nuchal-type fibroma; germline; next generation sequencing (NGS)

Submitted Feb 02, 2023. Accepted for publication Jul 27, 2023. Published online Sep 06, 2023.
doi: 10.21037/tp-23-60
View this article at: https://dx.doi.org/10.21037/tp-23-60

Introduction

Desmoid tumors (DTs), also known as desmoid-type fibromatosis or aggressive fibromatosis, is a rare soft tissue neoplasm characterized by a local aggressive and infiltrative growth (1). The incidence is approximately 5 cases per million with two peaks of incidences between the ages of 6 and 15 years and around 40 years, being more prevalent in women (2:1, female:male rate) (2).

DTs can arise in different sites classified into three groups located intra-abdominal, abdominal-wall and extra-abdominal (3). These neoplasms are characterized clinically by a variable and unpredictable course and can arise in many patients in the context of a hereditary cancer predisposition syndrome (4). Around 5–10% of patients who are diagnosed with DT have a pathogenic variant in the *APC* gene (5).

Nuchal-type fibroma is a benign tumor that develops from connective tissue and is usually located in the posterior neck. Other localizations are back, chest or shoulder. There

^ ORCID: Piedad Alba-Pavón, 0000-0002-5642-115X; Olatz Villate, 0000-0002-5574-837X.

are described several cases of nuchal-type fibroma associated to Gardner syndrome, a rare autosomal dominant syndrome caused by germline variants in the *APC* gene (6,7). Nuchal-type fibromas associated with Gardner syndrome are called Gardner-associated fibromas or Gardner fibromas (8).

Gardner syndrome is a variant of familial adenomatous polyposis (FAP) characterized by the presence of extracolonic manifestations including osteomas, dental abnormalities, epidermal cysts, and soft tissue tumors, particularly DTs. Gardner-associated fibromas may occur in pediatric patients as precursor lesions to the DTs of Gardner syndrome (8). Soft-tissue manifestation in the early ages may serve as the sentinel event leading to diagnostic suspicion of Gardner syndrome (9).

Kostakis *et al.* described a cohort of 107 patients with nuchal-type fibroma, of whom 18.7% had Gardner syndrome. In addition, these patients with Gardner syndrome were younger than the patients with sporadic fibroma (7). Gardner-associated fibromas usually have a higher recurrence after surgical excision. Some of these relapses can appear as DTs (10,11).

FAP is an autosomal dominant disease arising from a germline variation in the *APC* gene. FAP is characterized by the development of multiple colorectal adenomatous polyps during the second decade of life, that predisposes to colorectal cancer (9). There are other extraintestinal manifestations that can appear in childhood, such as DTs, which occur in approximately 10–25% of FAP patients in the context of Gardner syndrome (12,13). Identifying FAP in young patients is important for colonoscopic surveillance to prevent the development of colorectal tumors (14).

APC is considered a tumor suppressor gene on 5q21 and codes for a protein involved in the WNT pathway. The role of APC in cytoplasm is a negative regulation of the canonical WNT signaling pathway (15). APC interacts with β-catenin in the cytoplasm through β-catenin phosphorylation, ubiquitination and proteolytic degradation. All these facts occur in the cytosol. When APC function is lost, β-catenin is accumulated in the cell nuclei, regulating cell proliferation, differentiation and apoptosis (16).

FAP accounts for 1% of all colorectal cancer cases. Approximately 15–20% of FAP are caused by *APC de novo* mutations (17). FAP has been described patients with mosaic *APC* variants. However, this mosaicism is underdiagnosed and the number of mosaic carriers is expected to be higher (18,19).

According to several studies, extracolonic manifestations of polyposis syndromes are frequently associated with FAP and *APC* germline mutations.

Many other inherited adenomatous polyposis syndromes exist including *MUTYH* associated polyposis (MAP) with the presence of *MUTYH* germline mutations and polymerase proofreading associated polyposis (PPAP) with germline mutations in *POLD1* and *POLE* genes (20).

This study aimed to evaluate the spectrum of *APC* germline variants in pediatric patients diagnosed with nuchal-type fibroma and DTs that may be associated with Gardner syndrome. Moreover, we analyzed *MUTYH*, *POLD1* and *POLE* germline variants in the patients that present *APC* wild-type but have a family history of colon polyposis and colon cancer. We present this article in accordance with the MDAR reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-60/rc).

Methods

Study population

This study included five pediatric patients diagnosed with DTs or nuchal-type fibromas in the Hospital Universitario Cruces (Barakaldo, Spain) who were evaluated for genetic counseling between 2018–2020.

Germline *APC* gene testing was offered as a part of standard clinical care. *MUTYH*, *POLD1* and *POLE* genetic tests were performed in patients without *APC* germline pathogenic variants.

After performing genetic counseling, peripheral blood samples were collected from each patient. In addition, clinical information was obtained, such as personal and family history, histopathology findings, treatment response and patient follow-up. The clinical characteristics of the patients are shown in *Table 1*.

Ethical statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients' parents or legal guardians for publication of this report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. Ethical approval was granted by the Research Ethics Committee of the Hospital Universitario Cruces (No. E17/58).

Table 1 Clinical characteristics of the five patients and germline variants identified

Patient	Age at diagnosis (years)	Sex	Diagnosis	Localization	Family history	Personal background	Treatment	Clinical course	Relapse treatment	Germline analysis			
										Gene	Nucleotide variant	Amino acid variant	Clinical significance
1	14.9	Male	Nuchal-type fibroma and pilomatrixoma	Occipital region	No	Lipoma	Surgery	Alive with no evidence of disease	No	*POLD1*	c.2275G>A	p.Val759Ile	VUS
2	11.4	Male	DT	Shoulder	Yes	No	Surgery	Alive with no evidence of disease	No	Not found			
3	1.8	Male	Nuchal-type fibroma	Lumbar paravertebral region	No	No	Surgery	Alive with no evidence of disease	No	*POLD1*	c.353C>T	p.Ser118Phe	VUS
4	5.3	Female	Nuchal-type fibroma and pilomatrixoma	Cervical	No	No	Surgery	Local progression	Chemotherapy; pazopanib	*APC*	c.4611del	p.Glu1538Asnfs*27	Pathogenic
5	11.9	Female	DT	Cervical	Yes	Dentigerous cysts	Chemotherapy	Abdominal DTs	Chemotherapy; sulindac + tamoxifen; pazopanib; radiotherapy	*APC*	c.5826_5829del	p.Asp1942Glufs*27	Pathogenic

DT, desmoid tumor; VUS, variant of uncertain significance.

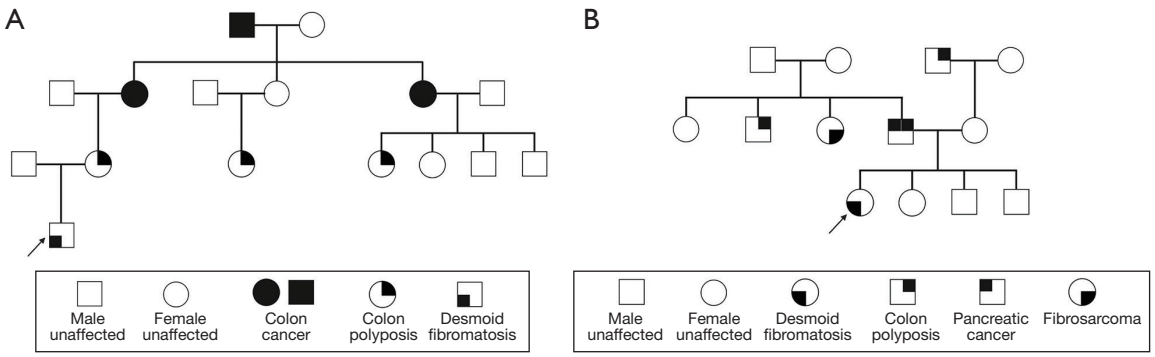

Figure 1 Pedigrees of patients with colorectal polyposis or colon cancer family history. (A) Patient 2 diagnosed with desmoid tumor. (B) Patient 5 diagnosed with desmoid tumor with an *APC* germline pathogenic variant. Proband is indicated by arrow.

Genetic testing

Genomic DNA was extracted from peripheral blood samples stored in EDTA using Magna Pure Compact Nucleic Acid Isolation Kit (Roche, Basel, Switzerland).

APC, *MUTYH*, *POLE* and *POLD1* genes were sequenced using Custom Hereditary Cancer Solution Kit (Sophia Genetics, Lausanne, Switzerland) in MiSeq v3 (Illumina, San Diego, CA, USA).

The identified variants were compared with different databases to analyze the clinical significance of the sequence differences found with respect to a reference genome (hg19). The variants were classified according to international recommendations (21) as pathogenic, likely pathogenic, benign, likely benign or of uncertain significance. Different web tools and databases were used: ClinVar, Varsome and LOVD. Variants of uncertain significance (VUS) were analyzed using different pathogenicity prediction tools based on sequence homology and conservation, genetic context, epigenetic information, protein features and integration of different prediction scores: Eigen, Eigen-PC, REVEL, PROVEAN, PrimateAI, CADD, DEOGEN2, CHASM, UMDPredictor, Polyphen-2 HDIV, Polyphen-2 HVAR, HOPE.

Results

Patient characteristics

A total of 5 patients were included in the study: three were diagnosed with nuchal-type fibromas and two with DTs. Two patients with fibromas also had pilomatrixomas. Two patients had a previous lesion diagnosed as lipoma and dentigerous cysts. The mean age at diagnosis was 11.4 years (range, 1.8–14.9 years). There were 2 females and 3 males. Clinical characteristics are described in *Table 1*. Two patients diagnosed with DTs had a family history of colorectal polyposis or colon cancer (patients 2 and 5). One patient had three relatives with colorectal polyps and three with colon cancer. The other patient had three family members with colorectal polyps, one of them with pancreas cancer and a relative with a fibrosarcoma. The pedigrees of patients with a family history are shown in *Figure 1*. All patients were treated with surgery at first line of treatment except one patient that was treated with chemotherapy. Tumors progressed in two of the patients (patients 4 and 5).

APC germline variants

Blood DNA was analyzed for the study of *APC* variants in the germline. Two pathogenic variants were identified in two female patients (patients 4 and 5) (*Table 1*, *Figure 2A*). *APC* c.4611del (p. Glu1538Asnfs*27) pathogenic variant was identified in patient 4. This patient had a nuchal-type fibroma and a pilomatrixoma in the parietal region. She underwent partial excision of the lesion. A conservative approach was decided initially and the lesion was stable for two years. Due to progression to DT, she was treated with low dose chemotherapy: methotrexate and vinorelbine (three months) without response, so it was changed to methotrexate plus vinblastine (one year) with partial response. Two months after the end of the treatment, tumor progression was observed and she was treated with pazopanib during eight months. However, tumor progressed after this tyrosine kinase inhibitor, and she was treated again with chemotherapy (methotrexate and vinblastine, during five months) without response, so oral vinorelbine monotherapy was decided as a bridge to cryotherapy.

The variant identified in the *APC* gene is classified as a

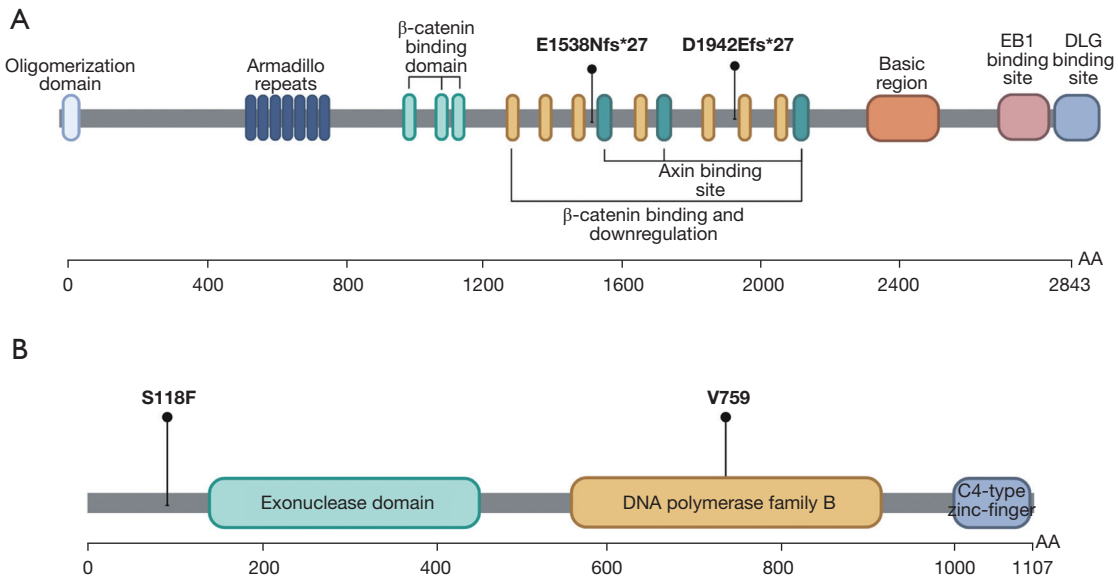

Figure 2 Germline variants identified in the analyzed patients. (A) *APC* germline pathogenic variants. (B) *POLD1* germline variants of uncertain significance. AA, amino acids; EB1, End-binding protein 1; DLG, Discs large protein.

pathogenic variant due to its effect on exon 16, resulting in a change of the reading frame in residue 1538 with a premature stop codon in residue 1565. To the best of our knowledge this variant has not been previously described in germline and it was not found in the progenitors. However, it has been described in many patients as a frameshift variant in the adjacent nucleotide (c.4612del) classified in ClinVar as pathogenic variant associated to FAP and Gardner syndrome (rs387906236).

An *APC* c.5826_5829del (p.Asp1942Glufs*27) pathogenic variant was found in patient 5. This patient had a familial history of cancer (*Figure 1B*) and was diagnosed with a cervical DT in childhood. She was treated with chemotherapy (vincristine, actinomycin and cyclophosphamide). After 21 years, this patient developed abdominal DTs. The genetic test was performed at this age. DTs were treated with tamoxifen and sulindac. Due to tumor progression, she was treated with pazopanib with a partial response. At the present, the patient had abdominal DTs treated with radiotherapy. The *APC* c.5826_5829del variant had been described and classified as a pathogenic variant (22,23).

POLD1 germline variants

Two VUSs were found in two male patients (patient 1 and patient 3) (*Table 1*, *Figure 2B*).

A *POLD1* c.2275G>A VUS was found in the patient 1, diagnosed with a nuchal-type fibroma and a pilomatrixoma (*Table 1*, *Figure 2B*). This patient had no familial history of colon cancer. He had a lipoma at birth in the same region of the fibroma. The lipoma was excised.

The *POLD1* c.2275G>A missense variant results in a change in the Valine 759 to an isoleucine. This variant has been reported in ClinVar as a benign variant, likely benign variant and VUS. The minor allele frequency (MAF) of this variant is 0.001842 according to GnomAD Exomes and it is described in Ashkenazi Jews with colorectal cancer, multiple polyps and other extracolonic tumors (24). POLD1 759 residue is part of the DNA polymerase type-B domain. Different prediction tools based on the structural changes introduced by an amino acid substitution predict this variant does not cause structural damage. However, other prediction tools predict this variant as likely pathogenic. Therefore, there are disagreements on its pathogenicity (Table S1).

Another *POLD1* VUS was identified in a patient diagnosed with a nuchal fibroma. He had no family history of cancer. The *POLD1* c.353C>T (p.Ser118Phe) variant has been reported in ClinVar and classified as a VUS. This variant is present in population databases with a GnomAD Exomes 0.0002. *POLD1* c.353C>T variant affected the Serine 118 that changes to Phenylalanine. This amino acid residue is not localized in a functional domain of the protein. However,

the mutant residue is bigger and more hydrophobic than the wild-type. Prediction tools do not agree on the potential impact of this missense change (Table S1).

Colonic surveillance

According to current ESPGHAN recommendations, colonic surveillance should begin between the ages 12 to 14 years. However, colonoscopy should be performed at any age in the event of rectal bleeding or mucous discharge (14).

Patients 1 and 4 are younger than 12 years old and they have not undergone colonoscopy yet. Patients 3 and 5 are under follow-up by gastroenterologist and they has no colorectal polyps on colonoscopy to date. Patient 2 has not been referred to the gastroenterologist because no germline variant has been identified in this patient.

APC, MUTYH, POLD1 and POLE germline pathogenic variants described in pediatric patients diagnosed with DTs

Nine patients diagnosed at pediatric age with DT and six with fibroma had been described in the literature with an *APC* pathogenic germline variant (*Table 2*). Eleven patients had a family history of tumor. Three patients developed medulloblastoma subsequently, two patients developed colon polyposis and one of them thyroid carcinoma. The incidence of these findings is limited by outcome data. Most of the patients would be expected to develop colon polyposis if long-term outcomes were available. All the variants identified in the *APC* gene except one were localized in exon 16.

No pathogenic germline variants in *MUTYH*, *POLD1* or *POLE* have been described in patients diagnosed with DTs in pediatric age.

Discussion

The appearance of fibromatous soft tissue lesions, DTs and nuchal-type fibromas, in childhood may be caused by germline mutations in genes associated with inherited adenomatous polyposis syndromes.

Gardner syndrome is a known variant of FAP. The name Gardner-associated fibroma was coined by one group of authors for nuchal-type fibroma arising in patients with Gardner's syndrome (10,30). The term Gardner fibroma has been described in the most recent WHO classification to define Gardner-associated fibroma (28). However, nuchal-type fibroma and Gardner fibroma are microscopically indistinguishable. It has been described that there are differences in the age groups, being Gardner fibroma associated to children (31,32). For this reason, the germline genetic study in the pediatric age is important.

Nuchal-type fibromas and DTs are distinct pathologic entities (28). However, both types of pathologies can appear in the pediatric age and may be associated with Gardner syndrome. In addition, DTs can arise in the same location of surgically excised Gardner-associated fibroma (8). Typically, these soft-tissue lesions occur first, alerting the clinician to the possibility of Gardner syndrome, because they occur before the development of intestinal polyps. It is important, therefore, to identify Gardner syndrome in early ages to prevent colorectal cancer (14).

We have analyzed variants in *APC*, *MUTYH*, *POLD1* and *POLE* genes in five patients diagnosed with DTs and nuchal-type fibromas. We have found two *APC* pathogenic germline variants in two different patients diagnosed with nuchal-type fibromas and DTs associated to Gardner syndrome. Both variants have been localized in *APC* exon 16. Several studies described that desmoid neoplasms are more frequent in patients with pathogenic/likely pathogenic variants localized after codon 1399. Moreover, 3' of codon 1399 variants are more symptomatic and more often lethal than 5' mutations in codon 400 (33). One of the identified variants (*APC* c.5826_5829del) has been associated with the development of DTs and Gardner fibroma in pediatric patients and colorectal adenomas in adults (22,23). To the best of our knowledge, the *APC* c.4611del variant has not been described in the germline. We found this variant in a patient with a Gardner fibroma that did not respond to treatment with chemotherapy and target therapy with pazopanib.

All reported pediatric patients with DTs associated with a hereditary syndrome, have *APC* germline pathogenic variants. Most of these extraintestinal neoplasms have been associated with *APC* germline mutations. However, some reports showed other extraintestinal manifestations like pilomatrixomas associated with *MUTYH* or *POLE* mutations too (34,35). Two patients in our cohort had pilomatrixomas, one had a VUS in *POLD1* gene and the other one had an *APC* pathogenic variant in the germline. In addition, some soft tissue neoplasms have been described in adult patients with *MUTYH* pathogenic variants in the germline (36,37).

We identified two *POLD1* VUSs in the germline in two different patients. POLD1 protein is the catalytic subunit of the DNA polymerase δ complex p125. POLD1 is involved

Table 2 *APC* germline variants described in the literature in patients with fibroma or desmoid tumors

Diagnosis	Age (years)	Sex	Gene	Nucleotide change	Amino acid change	Exon	Family history	Others subsequent manifestations	Reference
DT	14	Female	*APC*	c.4459dupA	p.Thr1487AsnfsTer27	16	Yes	NA	(25)
Gardner fibroma	16	Male	*APC*	c.4463dupT	p.Leu1488PhefsTer26	16	No	NA	(26)
DT	9	NA	*APC*	c.1577_1578insT	p.Met526IlefsTer11	13	Yes	Medulloblastoma	(27)
DT	13	NA	*APC*	c.3147G>A	p.Trp1049Ter	16	Yes	Medulloblastoma	(27)
DT	17	NA	*APC*	c.3189_3192del	p.Glu1064LysfsTer61	16	Yes	Medulloblastoma	(27)
Gardner fibroma	NA	NA	*APC*	c.4393_4394del	p.Ser1465TrpfsTer3	16	No	NA	(28)
Gardner fibroma	NA	NA	*APC*	c.3183_3187del	p.Gln1062Ter	16	No	NA	(28)
Gardner fibroma	NA	NA	chr.5q21.3_q22.3 del				No	NA	(26)
DT	15	Female	*APC*	c.3050_3053del	p.Asn1017MetfsTer4	16	Yes	Polyposis and thyroid carcinoma	(29)
DT	15	Female	*APC*	c.4216C>T	p.Gln1406Ter	16	Yes	NA	(29)
DT	1	Male	*APC*	c.4348C>T	p.Arg1450Ter	16	Yes	NA	(29)
Gardner fibroma	1	Male	*APC*	c.4687dup	p.Leu1563ProfsTer4	16	Yes	No	(22)
Gardner fibroma	1	Male	*APC*	c.5826_5829del	p.Asp1942GlufsTer27	16	Yes	No	(22)
DT	NA	Male	*APC*	c.4638_4642del	p.Asn1546LysfsTer11	16	Yes	Polyposis	(23)
DT	15	NA	*APC*	c.3920T>A	p.Ile1307Lys	16	Yes	NA	(23)

DT, desmoid tumor; NA, not available.

in DNA synthesis of the lagging strand during DNA replication, proofreading activity during polymerization and DNA repair (20). *POLD1* c.353C>T (p.Val759Ile) variant is localized in the DNA polymerase type-B domain. This variant has previously been described in a cohort of Ashkenazi Jewish subjects with multiple colorectal adenomas and early-onset mismatch repair proficient colorectal cancers. They identified a *POLD1* c.353C>T variant in eight unrelated individuals. Six of these patients had a family history of cancer. However, none of them developed a soft tissue neoplasm. The *POLD1* c.353C>T variant has been proposed to be a low-to-moderate risk founder mutation (24). No cases of DTs associated with *POLD1* germline mutations have been reported previously. The other variant identified in *POLD1* (c.353C>T) has been described in ClinVar as a VUS (ClinVar Variation Id: 239345). The role of this variant in disease is unknown.

No variants were identified in the genes analyzed in a patient with a family history of polyposis and colon cancer. It is possible that this family could have a variant in an intronic region of the analyzed genes (38) or have a pathogenic variant in another gene associated with hereditary colon cancer such as *CHEK2*, *AXIN2*, *CDH1*, *TP53*, *EPCAM* or mismatch repair genes (20). Some cases with DTs and colon cancer have been associated with *PTEN* or *TP53* germline mutations but these variants were associated with other neoplasms and clinical manifestations too (39,40). Double mutations in *APC* and *MSH2* genes were reported in a patient with adenomas and a DT (41). Further investigation about genetic risk of DTs and colon cancer development is necessary.

In this study, two germline pathogenic variants in *APC* and two germline VUSes in *POLD1* have been identified in four different patients diagnosed with DTs. Two patients

had a family history of colon cancer but we only identified an *APC* germline pathogenic variant in one of these patients. Further studies are necessary to identify and characterize germline variants associated with the development of DTs in a cancer predisposition syndrome context.

The two patients with *APC* germline pathogenic variants still have progressive lesions. DTs are known as aggressive and locally invasive neoplasms with difficult surgical cure (42). Currently, there are several studies focused on identifying effective treatment, such as γ-secretase inhibitors and cryoablation (5,43,44).

The identification of hereditary cancer predisposition syndromes in patients with DTs and nuchal-type fibromas is necessary for the correct clinical management and genetic counseling. Due to the risk of developing colon cancer, surveillance via lower gastrointestinal tract endoscopy is crucial in patients with *APC* germline mutations in a Gardner syndrome context (45). In addition, more studies to identify effective therapies for patients with progressing tumors are required.

Acknowledgments

Funding: This work was funded by Research Projects from Jesús de Gangoiti Barrera Foundation (Nos. FJGB18/004 and FJGB19/001), La Cuadri del Hospi (No. BC/A/17/008), EITB Media AND BIOEF, SAU (Nos. BIO20/CI/015/BCB and BIO20/CI/011/BCB) and the Basque Government Health Department (No. 2021111030).

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-60/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-60/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-60/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients' parents or legal guardians for publication of this report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. Ethical approval was granted by the Research Ethics Committee of the Hospital Universitario Cruces (No. E17/58).

References

1. Sakorafas GH, Nissotakis C, Peros G. Abdominal desmoid tumors. Surg Oncol 2007;16:131-42.
2. Eastley N, McCulloch T, Esler C, et al. Extra-abdominal desmoid fibromatosis: A review of management, current guidance and unanswered questions. Eur J Surg Oncol 2016;42:1071-83.
3. Peña S, Brickman T, StHilaire H, et al. Aggressive fibromatosis of the head and neck in the pediatric population. Int J Pediatr Otorhinolaryngol 2014;78:1-4.
4. Kasper B, Ströbel P, Hohenberger P. Desmoid tumors: clinical features and treatment options for advanced disease. Oncologist 2011;16:682-93.
5. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. Eur J Cancer 2020;127:96-107.
6. Diwan AH, Graves ED, King JA, et al. Nuchal-type fibroma in two related patients with Gardner's syndrome. Am J Surg Pathol 2000;24:1563-7.
7. Kostakis ID, Feretis T, Damaskos C, et al. Nuchal-type Fibroma: Single-Center Experience and Systematic Literature Review. In Vivo 2020;34:2217-23.
8. Coffin CM, Hornick JL, Zhou H, et al. Gardner fibroma: a clinicopathologic and immunohistochemical analysis of 45 patients with 57 fibromas. Am J Surg Pathol 2007;31:410-6.
9. Galiatsatos P, Foulkes WD. Familial adenomatous

polyposis. Am J Gastroenterol 2006;101:385-98.
10. Wehrli BM, Weiss SW, Yandow S, et al. Gardner-associated fibromas (GAF) in young patients: a distinct fibrous lesion that identifies unsuspected Gardner syndrome and risk for fibromatosis. Am J Surg Pathol 2001;25:645-51.
11. Kiessling P, Dowling E, Huang Y, et al. Identification of aggressive Gardner syndrome phenotype associated with a de novo APC variant, c.4666dup. Cold Spring Harb Mol Case Stud 2019;5:a003640.
12. Bertario L, Russo A, Sala P, et al. Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. Int J Cancer 2001;95:102-7.
13. Friedl W, Caspari R, Sengteller M, et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. Gut 2001;48:515-21.
14. Hyer W, Cohen S, Attard T, et al. Management of Familial Adenomatous Polyposis in Children and Adolescents: Position Paper From the ESPGHAN Polyposis Working Group. J Pediatr Gastroenterol Nutr 2019;68:428-41.
15. Munemitsu S, Albert I, Souza B, et al. Regulation of intracellular beta-catenin levels by the adenomatous polyposis coli (APC) tumor-suppressor protein. Proc Natl Acad Sci U S A 1995;92:3046-50.
16. Behrens J, Jerchow BA, Würtele M, et al. Functional interaction of an axin homolog, conductin, with beta-catenin, APC, and GSK3beta. Science 1998;280:596-9.
17. Buecher B. Colorectal adenomatous polyposis syndromes: Genetic determinism, clinical presentation and recommendations for care. Bull Cancer 2016;103:199-209.
18. Jansen AML, Goel A. Mosaicism in Patients With Colorectal Cancer or Polyposis Syndromes: A Systematic Review. Clin Gastroenterol Hepatol 2020;18:1949-60.
19. Rofes P, González S, Navarro M, et al. Paired Somatic-Germline Testing of 15 Polyposis and Colorectal Cancer-Predisposing Genes Highlights the Role of APC Mosaicism in de Novo Familial Adenomatous Polyposis. J Mol Diagn 2021;23:1452-9.
20. Talseth-Palmer BA. The genetic basis of colonic adenomatous polyposis syndromes. Hered Cancer Clin Pract 2017;15:5.
21. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
22. Vieira J, Pinto C, Afonso M, et al. Identification of previously unrecognized FAP in children with Gardner fibroma. Eur J Hum Genet 2015;23:715-8.
23. Bisgaard ML, Ripa RS, Bülow S. Mutation analysis of the adenomatous polyposis coli (APC) gene in Danish patients with familial adenomatous polyposis (FAP). Hum Mutat 2004;23:522.
24. Rosner G, Gluck N, Carmi S, et al. POLD1 and POLE Gene Mutations in Jewish Cohorts of Early-Onset Colorectal Cancer and of Multiple Colorectal Adenomas. Dis Colon Rectum 2018;61:1073-9.
25. Khider F, Cherbal F, Boumehdi AL, et al. Germline mutations of the adenomatous polyposis coli (APC) gene in Algerian familial adenomatous polyposis cohort: first report. Mol Biol Rep 2022;49:3823-37.
26. Signoroni S, Piozzi GN, Collini P, et al. Gardner-associated fibroma of the neck: role of a multidisciplinary evaluation for familial adenomatous polyposis diagnosis. Tumori 2021;107:NP73-6.
27. Surun A, Varlet P, Brugières L, et al. Medulloblastomas associated with an APC germline pathogenic variant share the good prognosis of CTNNB1-mutated medulloblastomas. Neuro Oncol 2020;22:128-38.
28. World Health Organization. Soft tissue and bone tumours. WHO Classification of Tumours, 5th Edition. Geneva: OMS; 2020.
29. Torrezan GT, da Silva FC, Santos EM, et al. Mutational spectrum of the APC and MUTYH genes and genotype-phenotype correlations in Brazilian FAP, AFAP, and MAP patients. Orphanet J Rare Dis 2013;8:54.
30. Michal M, Boudova L, Mukensnabl P. Gardner's syndrome associated fibromas. Pathol Int 2004;54:523-6.
31. Dahl NA, Sheil A, Knapke S, et al. Gardner Fibroma: Clinical and Histopathologic Implications of Germline APC Mutation Association. J Pediatr Hematol Oncol 2016;38:e154-7.
32. Balachandran K, Allen PW, MacCormac LB. Nuchal fibroma. A clinicopathological study of nine cases. Am J Surg Pathol 1995;19:313-7.
33. Church J, Xhaja X, LaGuardia L, et al. Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum 2015;58:444-8.
34. Baglioni S, Melean G, Gensini F, et al. A kindred with MYH-associated polyposis and pilomatricomas. Am J Med Genet A 2005;134A:212-4.
35. Wimmer K, Beilken A, Nustede R, et al. A novel germline POLE mutation causes an early onset cancer prone syndrome mimicking constitutional mismatch repair deficiency. Fam Cancer 2017;16:67-71.

36. Wang J, Jia N, Lin Q, et al. Clinicopathological and molecular characteristics of abdominal desmoid tumors in the Chinese population: A single-center report of 15 cases. Oncol Lett 2019;18:6443-50.
37. de Ferro SM, Suspiro A, Fidalgo P, et al. Aggressive phenotype of MYH-associated polyposis with jejunal cancer and intra-abdominal desmoid tumor: report of a case. Dis Colon Rectum 2009;52:742-5.
38. Szekely AM, Chen YH, Zhang C, et al. Werner protein recruits DNA polymerase delta to the nucleolus. Proc Natl Acad Sci U S A 2000;97:11365-70.
39. Kato N, Kimura K, Sugawara H, et al. Germline mutation of the PTEN gene in a Japanese patient with Cowden's disease. Int J Oncol 2001;18:1017-22.
40. Cloutier JM, Shalin SC, Lindberg M, et al. Cutaneous pleomorphic fibromas arising in patients with germline TP53 mutations. J Cutan Pathol 2020;47:734-41.
41. Soravia C, DeLozier CD, Dobbie Z, et al. Double frameshift mutations in APC and MSH2 in the same individual. Int J Colorectal Dis 2005;20:466-70.
42. Wang Z, Wu J, Lv A, et al. En bloc resection for intra-abdominal/retroperitoneal desmoid-type fibromatosis with adjacent organ involvement: A case series and literature review. Biosci Trends 2018;12:620-6.
43. Riedel RF, Agulnik M. Evolving strategies for management of desmoid tumor. Cancer 2022;128:3027-40.
44. Kujak JL, Liu PT, Johnson GB, et al. Early experience with percutaneous cryoablation of extra-abdominal desmoid tumors. Skeletal Radiol 2010;39:175-82.
45. Charifa A, Jamil RT, Zhang X. Gardner Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.

Cite this article as: Alba-Pavón P, Astigarraga I, Alaña L, Llano-Rivas I, Gener B, Mosteiro L, López-Almaraz R, Echebarria-Barona A, Villate O. Analysis of germline variants in pediatric patients diagnosed with desmoid tumors and nuchal-type fibromas. Transl Pediatr 2023;12(9):1715-1724. doi: 10.21037/tp-23-60