

Risk of Desmoid Tumor Based on APC Pathogenic Variant Location and Surgical History in Familial Adenomatous Polyposis: A U.S. Community Cohort Study

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Short Report

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Abstract

Desmoid tumors (DT) are a leading cause of morbidity and mortality in patients with familial adenomatous polyposis (FAP), yet available data on DT risk remain limited and have been largely derived from European registries or tertiary referral centers. Risk in community-based U.S. populations is poorly defined, which hinders presurgical counseling. We conducted a retrospective cohort study of patients with pathogenic or likely pathogenic variants (PV/LPV) in *APC* identified through the Kaiser Permanente Northern California Genetics Database, a community-based system serving 4.6 million members. We evaluated the association of *APC* PV/LPV location and prior abdominal surgery with DT risk using multivariable logistic regression, adjusting for age, sex, race and ethnicity, and family history. Among 328 patients with FAP, 36 (11.0%) developed DT. DT risk was highest when the *APC* variant was centrally located (codon 600–1600), and family history was independently associated with increased risk (adjusted odds ratio [aOR] 4.50; 95% confidence interval [CI] 1.12–18.14). All colorectal surgeries were associated with a significantly elevated DT risk: end ileostomy (aOR 12.60; 2.22–71.46), subtotal colectomy with ileorectal anastomosis (aOR 9.27; 1.72–49.91), and total proctocolectomy with ileal pouch-anal anastomosis (aOR 11.19; 2.19–57.05). In contrast, non-colorectal surgery was not associated with increased risk (aOR 0.90). In this large community-based U.S. cohort, central *APC* variant location, family history, and colorectal surgery were associated with increased DT risk. Our findings extend the current literature on DT risk in FAP and help refine presurgical risk-stratification and counseling for these patients.

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome caused by pathogenic variants or likely pathogenic variants (PV/LPV) in the *APC* gene, with a high lifetime risk for colorectal cancer (CRC) [1]. Desmoid tumors (DTs) have been recognized as a leading cause of morbidity and mortality in this population [2, 3]. Established DT risk factors include prior abdominal surgery, certain locations of PV/LPV in *APC*, and family history of DT [4–6]. However, a majority of studies on DT risk are derived from either large registries (particularly from Europe) or tertiary referral centers. In contrast, risk of DTs in community-based U.S. populations remains poorly defined, which hinders presurgical counseling and decision-making in FAP patients [7]. To address this knowledge gap, we evaluated the association of *APC* PV/LPV locations and prior history of abdominal surgeries with the DT risk in a community-based FAP cohort in the U.S.

Methods

We conducted a retrospective cohort study of patients with PV/LPVs in *APC* at Kaiser Permanente Northern California (KPNC), a large community-based healthcare system with 4.6 million members. Patients with FAP and the location of *APC* PV/LPVs were identified through the KPNC Genetics Database and confirmed by manual review of medical records. DTs were confirmed by cross-sectional imaging studies, pathology, or both. History of abdominal surgeries was categorized as no prior surgery, subtotal

colectomy with ileorectal anastomosis (STC-IRA), total proctocolectomy with ileal pouch-anal anastomosis (TPC-IPAA), end ileostomy, or non-colorectal surgeries (labeled as “other”). Surgical approaches were also classified as open or laparoscopic. Firth-penalized multivariable logistic regression measured adjusted odds ratios (aOR) with 95% confidence intervals (CI) for DT, adjusting for age at APC PV/LPV diagnosis, sex, race and ethnicity, and family history of DT. We conducted three logistic regression models: Model 1 assessed the overall surgical approach (open vs. laparoscopic); Model 2 assessed surgery type (ileostomy, STC-IRA, TPC-IPAA, or other); and Model 3 stratified surgical history based on both surgical approach and type. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Results

Of the 328 patients with FAP, 36 (11.0%) developed DT (Table 1). The distributions of PV/LPV in APC with or without DT are shown in Fig. 1. The risk of DT peaked at APC codon 600–800 and at 1200–1600. Among the demographic variables evaluated, only the family history was associated with an increased risk (aOR 4.50, 1.12–18.14; $P = 0.03$) (Table 2).

Table 1
Baseline characteristics of patients with familial adenomatous polyposis stratified by desmoid tumor status

Characteristic	Total (N = 328) N (%)	No DT (N = 292) N (%)	DT (N = 36) N (%)
Age, years			
Median (IQR)	31.5 (24.0–46.0)	33.0 (23.5–46.5)	27.0 (24.0–31.0)
Sex			
Female	166 (50.6)	147 (50.3)	19 (52.8)
Male	162 (49.4)	145 (49.7)	17 (47.2)
Race and ethnicity			
White	164 (50.0)	148 (50.7)	16 (44.4)
Hispanic	93 (28.4)	78 (26.7)	15 (41.7)
Asian	34 (10.4)	31 (10.6)	3 (8.3)
Black	15 (4.6)	13 (4.5)	2 (5.6)
Other	22 (6.7)	22 (7.5)	0 (0)
Location of APC PV/LPV (codon)			
≤ 400	99 (30.2)	96 (32.9)	3 (8.3)
401–1399	91 (27.7)	75 (25.7)	16 (44.4)
≥ 1400	23 (7.0)	21 (7.2)	2 (5.6)
Large deletion	17 (5.2)	16 (5.5)	1 (2.8)
Unknown	98 (29.9)	84 (28.8)	14 (38.9)
Family history of DT	13 (4.0)	8 (2.7)	5 (13.9)
Abbreviations: DT, desmoid tumor; IQR, interquartile range, PV/LPV: pathogenic/likely pathogenic variant			

Note: Age was defined as the age when APC PV/LPV was identified via germline testing.

Table 2
Adjusted odds ratios for desmoid tumors in patients with familial adenomatous polyposis based on surgical history.

Variable	aOR	95% CI	P value
MODEL 1			
Age, years^a			
< 50 (ref)	1.00		
50–69	0.64	0.18–2.22	0.48
70+	0.23	0.011–4.88	0.35
Other ^b	0.63	0.28–1.41	0.26
Sex			
Female	1.04	0.51–2.11	0.91
Male (ref)	1.00		
Race and ethnicity			
Asian	0.81	0.23–2.83	0.74
Black	1.13	0.23–5.47	0.88
Hispanic	1.58	0.71–3.56	0.27
Non-Hispanic White (ref)	1.00		
Other	0.19	0.011–3.54	0.28
Family history			
Yes	4.50	1.12–18.14	0.03
No (ref)	1.00		
Surgery approach			
No surgery (ref)	1.00		
Laparoscopic	0.42	0.02–9.32	0.59
Open	14.10	2.81–70.68	0.001
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; STC-IRA, subtotal colectomy with ileorectal anastomosis; TPC-IPAA, total proctocolectomy with ileal pouch-anal anastomosis.			
^a Age here was defined as the age of diagnosis of APC PV/LPV.			
^b The location of APC PV/LPV was unknown.			

Variable	aOR	95% CI	P value
MODEL 1			
MODEL 2: Surgery type			
No surgery (ref)	1.00		
Ileostomy	12.60	2.22–71.46	0.004
STC-IRA	9.27	1.72–49.91	0.01
TPC-IPAA	11.19	2.19–57.05	0.004
Other	0.90	0.05–16.96	0.95
MODEL 3: Surgery type and approach			
No surgery (ref)	1.00		
Ileostomy (laparoscopic)	11.31	1.36–94.04	0.02
Ileostomy (open)	15.32	2.44–96.19	0.004
STC-IRA (laparoscopic)	5.55	0.83–36.92	0.08
STC-IRA (open)	17.71	2.90–108.38	0.002
TPC-IPAA (laparoscopic)	10.77	1.87–62.21	0.008
TPC-IPAA (open)	13.14	2.43–71.16	0.003
Other (laparoscopic)	1.52	0.06–36.49	0.80
Other (open)	2.06	0.10–41.50	0.64
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; STC-IRA, subtotal colectomy with ileorectal anastomosis; TPC-IPAA, total proctocolectomy with ileal pouch-anal anastomosis.			
^a Age here was defined as the age of diagnosis of APC PV/LPV.			
^b The location of APC PV/LPV was unknown.			

Note: Firth-penalized multivariable logistic regression models were adjusted for age, sex, race and ethnicity, and family history of DT. P values <0.05 are shown in bold fonts.

Regarding history of abdominal surgery, all three types of colorectal surgeries were associated with increased risk of DT: ileostomy (aOR 12.60; 2.22–71.46), STC-IRA (aOR 9.27, 1.72–49.91), and TPC-IPAA (aOR 11.19; 2.19–57.05); non-colorectal surgery was not associated with increased risk (aOR 0.90). When stratified by both surgical approach (open vs. laparoscopic) and subtypes, both open and laparoscopic ileostomy or TPC-IPAA were associated with significantly increased risk of DT; open STC-IRA was also associated with an increased risk while laparoscopic STC-IRA did not reach statistical

significance ($P = 0.08$). Non-colorectal surgeries, whether by open or laparoscopic approach, were not associated with an increased risk (Table 2).

Discussion

In a large community-based U.S. population, PV/LPVs in the central location of the *APC* gene, family history of DT, and all types of colorectal surgery were associated with an increased risk of DT in patients with FAP, while non-colorectal surgeries were not associated with an increased risk. Our findings extend the available literature on DT risk in FAP and will help inform presurgical counseling and decision-making in patients with FAP.

Several prior studies reported an increased risk of DT when the *APC* variants are distal (or at 3') to codon 1399 or codon 1444 compared with proximally located *APC* variants [4, 5, 8]. However, even in these reports, a substantial proportion of DT cases occurred in patients with central *APC* variants (e.g., between 1000 and 1399) and using one division point only provided limited guidance for risk stratification. In our study, no DT occurred beyond codon 1541 while the DT risk was higher when the *APC* variant was located in the central region (particularly in codon range 600–1600) (Fig. 1c). This finding is consistent with studies using the Heidelberg Polyposis Register in Germany [9] and St. Mark's Polyposis Registry for the United Kingdom [6]. Taken together, the central *APC* location (particularly 1000–1600) seems to confer the highest risk of DT.

Data regarding the effect of surgical history on DT risk in FAP are also conflicting. Two meta-analyses showed no significant differences in DT risk between IRA and IPAA [10, 11]. However, a recent international cohort study showed a significantly higher DT risk associated with IPAA compared with IRA [12]. In the current study, all types of colorectal surgeries including STC-IRA, TPC-IPAA, and ileostomy were associated with a significantly elevated DT risk, and the risk was more pronounced with the open approach. We did not observe an increased DT risk associated with non-colorectal surgeries.

To our knowledge, this is the first study on DT risk in FAP in a large community-based U.S. population, with minimal referral bias. Our study has several limitations. First, the locations of *APC* PV/LPV were not retrievable in 29.9% of patients with FAP, which precludes the evaluation of genotype-phenotype correlation in these patients. However, most of these 29.9% of patients had germline testing more than 2 decades ago, and those with available *APC* PV/LPV information represented consecutive FAP patients who were tested in more recent years. There is no compelling reason to suspect the germline testing findings in earlier years would be significantly different from the more recent findings. Second, despite our data being derived from a large community-based population, the sample size of the cohort remains limited, which reduced the statistical power and precision of our analyses, particularly in stratified analyses by surgical history.

In summary, in this FAP cohort derived from a large, community-based U.S. population, *APC* PV/LPV in the central *APC* region, family history of DT, and history of colorectal surgeries were associated with

significantly elevated DT risk. Our findings refine the understanding of DT risk in community-based U.S. practice and inform presurgical counseling on DT risk in the real-world practice setting.

Declarations

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Competing interests: The authors have no relevant competing interests to disclose.

Ethics approval This study was approved by the Kaiser Permanente Northern California Institutional Review Board, which granted a waiver of informed consent given the retrospective design. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Consent to participate The Kaiser Permanente Northern California Institutional Review Board granted a waiver of informed consent given the retrospective design of the study.

Consent to publish Not applicable. This study reports aggregate data and contains no individually identifiable information.

Data availability Deidentified data are available from the corresponding author upon reasonable request, subject to institutional data-sharing policies.

Author contributions Prakash Thomas contributed to study design, data collection, analysis and interpretation, and drafting of the manuscript. Holly Carwana contributed to data collection. Sheng-Fang Jiang performed the statistical analysis and revised the manuscript. Janet Song contributed to data collection. Dan Li contributed to study conception, design, supervision, and drafting and revision of the manuscript. All authors reviewed and approved the final submitted manuscript.

References

1. Lynch HT, de la Chapelle A (2003) Hereditary colorectal cancer. *N Engl J Med* 348:919–932
2. Vasen HF, Tomlinson I, Castells A (2015) Clinical management of hereditary colorectal cancer syndromes. *Nat Rev Gastroenterol Hepatol* 12:88–97
3. Nieuwenhuis MH, Casparie M, Mathus-Vliegen LM et al (2011) A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. *Int J Cancer* 129:256–261
4. Sinha A, Tekkis PP, Gibbons DC et al (2011) Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. *Colorectal Dis* 13:1222–1229
5. Church J, Xhaja X, LaGuardia L et al (2015) Desmoids and genotype in familial adenomatous polyposis. *Dis Colon Rectum* 58:444–448

6. Sturt NJ, Gallagher MC, Bassett P et al (2004) Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline *APC* mutation. *Gut* 53:1832–1836
7. Steinberger AE, Westfal ML, Wise PE (2024) Surgical decision-making in familial adenomatous polyposis. *Clin Colon Rectal Surg* 37:191–197
8. Bertario L, Russo A, Sala P et al (2001) Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. *Int J Cancer* 95:102–107
9. Schiessling S, Kihm M, Ganschow P et al (2013) Desmoid tumour biology in patients with familial adenomatous polyposis coli. *Br J Surg* 100:694–703
10. Aelvoet AS, Struik D, Bastiaansen BAJ et al (2022) Colectomy and desmoid tumours in familial adenomatous polyposis: a systematic review and meta-analysis. *Fam Cancer* 21:429–439
11. Xie M, Chen Y, Wei W et al (2020) Does ileoanal pouch surgery increase the risk of desmoid in patients with familial adenomatous polyposis? *Int J Colorectal Dis* 35:1599–1605
12. Aelvoet AS, Pellise M, Miedema TN et al (2024) Development of desmoid tumors after ileorectal anastomosis versus ileal pouch-anal anastomosis in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 22:2319–2326

Figures

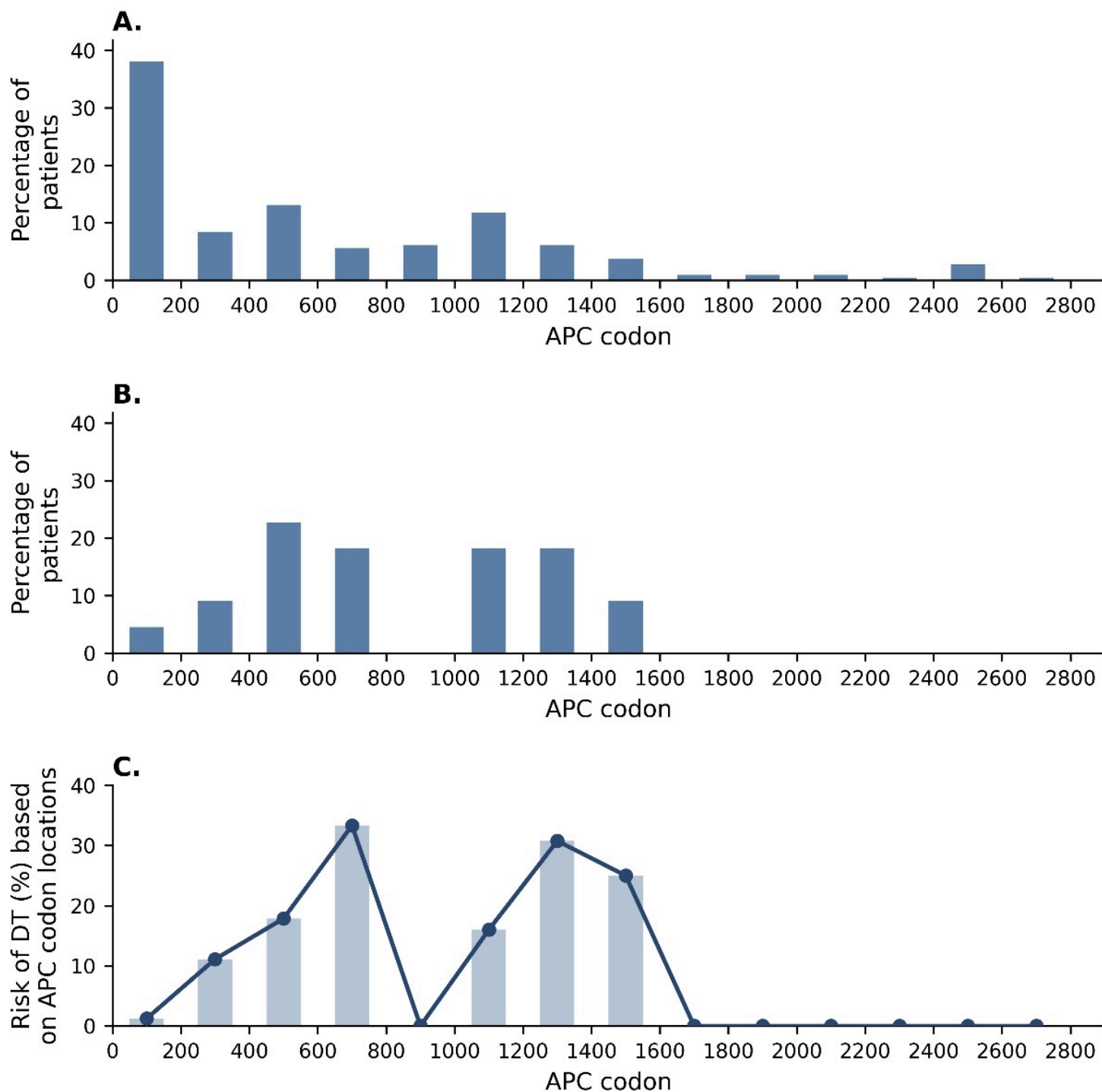


Figure 1

Distribution of *APC* pathogenic/likely pathogenic variants in patients with familial adenomatous polyposis, stratified by the diagnosis of desmoid tumors. **A.** All patients with FAP with a known *APC* PV/LPV location (n = 213); patients with unknown PV/LPV location or large deletions are not displayed. **B.** FAP patients who developed DTs (n = 22); patients with unknown *APC* PV/LPV location are not displayed. **C.** Risk of DT (%) based on *APC* codon location, measured as the number of patients who developed DTs divided by the total number of FAP patients in each *APC* location (per 200-codon

segment). Abbreviations: FAP, familial adenomatous polyposis; DT, desmoid tumor; PV/LPV, pathogenic/likely pathogenic variant