

How does desmoid risk influence surgical management in FAP?¹

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1. Data previously published as Sturt et al. Gut
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Introduction

- Desmoid tumours are non-metastasising but aggressive tumours of fibroblast origin which occur in association with FAP
- Their incidence in FAP is between 10-20%
- There is increasingly good evidence that FAP-associated desmoids are stimulated into growth by abdominal surgery (usually prophylactic colectomy)

Introduction

- Desmoid tumours are one of the commonest causes of death in patients who have undergone colectomy
- The average age of death in such cases is young (35 years in one study²)
- For this reason we performed a detailed analysis of risk factors for desmoid development in FAP

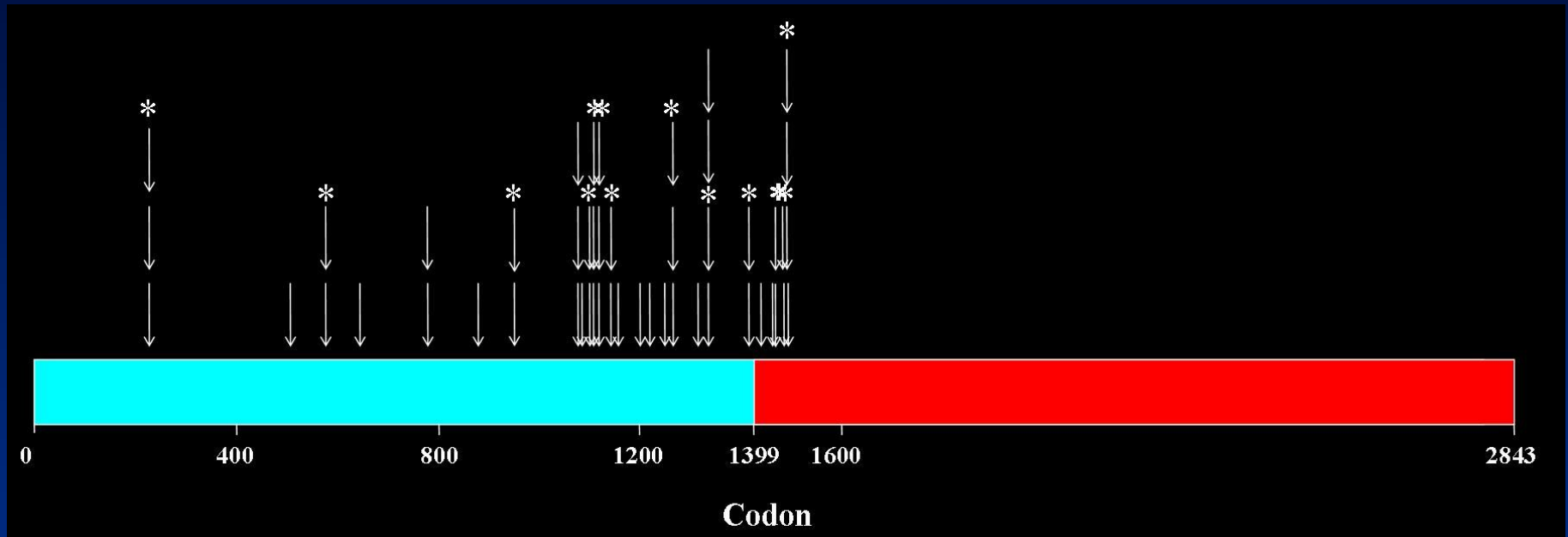
Methods

- We examined the records of all the patients who have attended the Polyposis Registry in whom the germline APC mutation is known (excluding those who were the only FAP positive members of their family)
- We determined single or multiple desmoid occurrence based on position of germline APC mutation, family history of desmoid disease, gender and history of previous abdominal surgery

Results

- The APC germline mutation was known in 320 individuals from 84 families
- In 78 families the APC germline mutation was 5' (< codon 1399) and in 6 it was 3' (93 vs. 7%)
- The total prevalence of desmoid disease was 16% (50/320 patients)

Position of APC mutations in patients with desmoids



- Arrows below * indicate affected members of the same family

Variable	Group	Odds Ratio (95% CI)	p value
Mutation Location	Before 1399	1	0.03
	After 1399	7.19 (1.27, 40.67)	
Proportion of other FAP+ve family members with desmoids	None	1	0.001
	1-49%	3.25 (0.76, 13.87)	
	50%+	7.66 (2.53, 23.25)	
Gender	Male	1	0.04
	Female	2.15 (1.02, 4.65)	
History of abdominal surgery	No	1	0.35
	Yes	2.02 (0.46, 8.90)	

Results

- Multivariate analysis confirmed the explanatory variables to be strong independent predictors of desmoid occurrence
- Thus, family history of desmoids is a major risk factor for desmoid development even when the germline APC mutation is 5'

Results

- If a single desmoid was expected to arise with a frequency of 14% in patients with 5' mutations then multiple tumours should be expected to account for 14% of this cohort
- Actual frequency was 45% (p value <0.001)
- A family history of multiple desmoids and a 3' APC germline mutation also strongly predisposed to multiple desmoid development (p<0.001 in both cases)

Discussion

- This study concurs with many previous investigations which have found an increased desmoid risk in patients with a 3' germline APC mutation, and in women
- It also provides evidence that family history is an independent risk factor (also noted by Bertario et al.³), suggesting the existence of further genes which modify desmoid risk

How should this evidence influence surgical management of the colon?

- Previous studies have shown that patients with a 3' germline mutation tend to have a sparse colorectal phenotype⁴
- These patients have a very high risk of subsequent desmoid development
- Therefore, should these patients should be managed by chemoprevention and surveillance, resorting to colectomy only if polyp burden or dysplasia becomes severe?

How should this evidence influence surgical management of the colon?

- Patients with a 5' germline mutation and a strong family history are also at very high risk of desmoid development
- However, these patients are more likely to have a dense colonic phenotype, particularly those with a germline mutation close to codon 1300

How should this evidence influence surgical management of the colon?

- In these patients we believe it may be worth undertaking a study into the effects of non-steroidal drugs (e.g. sulindac) and anti-oestrogens (e.g. high-dose tamoxifen) given at the time of colectomy as attempted prophylaxis against the subsequent development of desmoid disease

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