Original article

Genotype-defined cancer risk in juvenile polyposis syndrome

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Background: **Germline mutations in *SMAD4* and *BMPR1A* disrupt the transforming growth factor β signal transduction pathway, and are associated with juvenile polyposis syndrome. The effect of genotype on the pattern of disease in this syndrome is unknown. This study evaluated the differential impact of *SMAD4* and *BMPR1A* gene mutations on cancer risk and oncological phenotype in patients with juvenile polyposis syndrome.**

Methods: **Patients with juvenile polyposis syndrome and germline *SMAD4* or *BMPR1A* mutations were identified from a prospectively maintained institutional registry. Medical records were reviewed and the clinical patterns of disease were analysed.**

Results: **Thirty-five patients had germline mutations in either *BMPR1A* (8 patients) or *SMAD4* (27). Median follow-up was 11 years. Colonic phenotype was similar between patients with *SMAD4* and *BMPR1A* mutations, whereas *SMAD4* mutations were associated with larger polyp numbers (number of patients with 50 or more gastric polyps: 14 *versus* 0 respectively). The numbers of patients with rectal polyps was comparable between *BMPR1A* and *SMAD4* mutation carriers (5 *versus* 17). No patient was diagnosed with cancer in the *BMPR1A* group, whereas four men with a *SMAD4* mutation developed gastrointestinal (3) or extraintestinal (1) cancer. The gastrointestinal cancer risk in patients with juvenile polyposis syndrome and a *SMAD4* mutation was 11 per cent (3 of 27).**

Conclusion: **The *SMAD4* genotype is associated with a more aggressive upper gastrointestinal malignancy risk in juvenile polyposis syndrome.**

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Introduction

Juvenile polyposis syndrome (JPS) is a clinically and genetically heterogeneous condition characterized by predisposition to hamartomatous polyps in the gastrointestinal tract[1]. Polyps can be found in the stomach, small intestine, colon and rectum[2]. In the majority of patients with JPS, germline mutations in one of two genes involved in the transforming growth factor (TGF) β signal transduction pathway can be identified: *SMAD4* or *BMPR1A* (bone morphogenetic protein receptor type Ia)[3–5]. In addition to intestinal hamartomatous polyposis, approximately 20 per cent of affected patients have congenital anomalies, including heart defects, cleft lip or palate and malrotation[6]. Hereditary haemorrhagic telangiectasia (HHT) is usually seen only in patients with JPS who have a *SMAD4* mutation[7], and has been described as the JPS–HHT overlap syndrome[8]. Epistaxis and asthma are the most common symptoms in patients with JPS–HHT overlap[9]. Recent reports[9,10] showed an association between mutations in *SMAD4* and *BMPR1A* and gastrointestinal cancer, as well as profuse polyposis. The cumulative lifetime risk of gastrointestinal cancer in patients with JPS varies between 9 and 50 per cent[10,11]. However, little is known about the way in which gastrointestinal phenotype, cancer development and oncological outcomes vary according to genotype in patients with JPS[12]. This study investigated the impact of genotype on cancer risk and oncological phenotype in patients with JPS with a *SMAD4* or *BMPR1A* gene mutation.

Methods

After obtaining approval from the institutional review board (IRB), patients with JPS were identified from the IRB-approved, prospectively maintained David G. Jagelman Inherited Colorectal Cancer Registries in the Sanford R. Weiss, M.D. Center for Hereditary Colorectal Neoplasia. Only patients who had either a *SMAD4* or *BMPR1A* mutation were included. Patients who had not undergone genetic testing or in whom no germline mutation could be identified were excluded. Medical records were reviewed to obtain information on cancer history, patient characteristics, operations, and gastric and colonic polyp counts. The development of cancer and dysplastic gastrointestinal polyps in any part of the body was noted. Colorectal and gastric polyposis phenotype was graded (less than 50 polyps, 50 or more polyps) based on the highest polyp number detected during surveillance.

In the authors' clinical practice, intervals of endoscopic surveillance vary between 1 and 3 years according to disease phenotype. Genetic testing is recommended to all patients at the time of genetic counselling. Total colectomy with ileorectal anastomosis is warranted if severe colonic polyposis with mild rectal involvement (20 or fewer polyps) is present. When the whole colon and rectum is severely affected, total proctocolectomy with ileal pouch–anal anastomosis (IPAA) is indicated[7].

Statistical analysis

Continuous data are reported as median (range). Comparisons of *SMAD4* and *BMPR1A* groups were performed using χ^2 or Fisher's exact tests for categorical data, and the Wilcoxon rank sum test for quantitative data. A level of $\alpha = 0{\cdot}05$ was used to establish statistical significance of individual P values.

Results

Thirty-five patients with JPS had either a *BMPR1A* (8) or *SMAD4* (27) mutation. All patients except one with a *SMAD4* mutation had the clinical characteristics of JPS[13]. The patient with no clinical signs of JPS had a family history of JPS–HHT overlap syndrome. His genetic test was performed at age 3 years and he had been under surveillance for 6 years. He had been diagnosed with an intrapulmonary shunt, suggesting an arteriovenous malformation.

Four patients in the *BMPR1A* group were related to two families and 20 patients in the *SMAD4* group were related to six families. The other patients were not related. Median age at the time of diagnosis was 17 (3–65) years. Overall median follow-up after diagnosis of JPS was 11 (1–33) years. Age, sex, family history and follow-up were comparable between the genotypes (*Table 1*).

Disease phenotype

Colonic phenotype was similar between the *BMPR1A* and *SMAD4* genotypes (3 *versus* 14 patients respectively with at least 50 polyps, 5 *versus* 11 patients with 1–49 polyps, 0 *versus* 1 patient with no polyps, 0 *versus* 1 patient with unknown gastrointestinal phenotype; $P = 0{\cdot}683$), as was the number of patients with rectal polyps (5 *versus* 17 respectively; $P > 0{\cdot}999$). However, *SMAD4* mutations were associated with higher gastric polyp numbers (0 *versus* 14 patients in *BMPR1A* and *SMAD4* groups respectively with at least 50 polyps, 5 *versus* 9 patients with 1–49 polyps, 0 *versus* 1 patient with no polyps, 3 *versus* 3 patients with unknown gastrointestinal phenotype; $P = 0{\cdot}041$).

The numbers of tubular (3 *versus* 7 in *BMPR1A* and *SMAD4* groups; $P = 0{\cdot}661$) and tubulovillous (0 *versus* 3 respectively; $P > 0{\cdot}999$) adenomas removed endoscopically during follow-up were similar between the groups. High-grade dysplasia was rare, found in one patient in each genotype group ($P = 0{\cdot}410$).

In addition to routine lower gastrointestinal tract endoscopy, 13 capsule endoscopies, two push enteroscopies and one balloon enteroscopy were performed. Small bowel juvenile polyps were diagnosed in 14 patients with *SMAD4* and two with *BMPR1A* mutations ($P = 0{\cdot}244$). Locations of the small bowel polyps were: duodenum (7 patients; range 0·2–2·5 cm), jejunum (1 patient; multiple, range 0·5–0·7 cm), ileum (3 patients; range 0·2–0·8 cm) and unknown location (4 patients; size unknown). One patient

Table 1 Demographic and disease data

	Overall ($n = 35$)	*BMPR1A* ($n = 8$)	*SMAD4* ($n = 27$)	P†
Age at time of diagnosis (years)*	17 (3–65)	18 (12–20)	17 (3–65)	0·925‡
Sex ratio (F : M)	14 : 21	4 : 4	10 : 17	0·511
Family history of JPS	29	5	24	0·117
Follow-up after diagnosis (years)*	11 (1–33)	6 (1–23)	11 (1–33)	0·193‡
Cancer-related death	3	0	3	> 0·999

*Values are median (range). JPS, juvenile polyposis syndrome. †Fisher's exact test, except ‡Wilcoxon rank sum test.

Table 2 Primary and secondary operations for polyps

	Overall ($n = 35$)	*BMPR1A* ($n = 8$)	*SMAD4* ($n = 27$)	*P*§
No gastrointestinal surgery*	11	3	8	0·686
Primary colorectal operation				0·102
RP-IPAA	5	3	2	
Subtotal/total colectomy	13	2	11	
Segmental colectomy	2	0	2	
Total gastrectomy†	7	0	7	0·166
Secondary colorectal operation				–
RP-IPAA	3	0	3	
Transanal excision‡	1	0	1	

*One patient with a *SMAD4* mutation underwent orchidectomy and right frontal mass excision, but no gastrointestinal resection. †Three patients had total gastrectomy and colonic resection. ‡Low rectal polyp excision for low-grade dysplasia with coexisting neuroendocrine tumour. RP-IPAA, restorative proctocolectomy with ileal pouch–anal anastomosis. §Fisher's exact test.

Table 3 Patient characteristics and follow-up of *SMAD4* mutation carriers with cancer

	No. of patients*
Age at time of cancer diagnosis (years)†	38 (29–70)
Follow-up (years)†	
After diagnosis of JPS	15 (2–33)
After diagnosis of cancer	2 (1–3)
Additional gastrointestinal disorder	
Ulcerative colitis	1
Operations before diagnosis of cancer	
Subtotal colectomy	2
Ileocolectomy	1
Types and stages of cancer	
Rectal neuroendocrine tumour (T2; G1 in WHO 2010 classification) and gastric adenocarcinoma (stage IV)	1
Gastric carcinoma (stage IV)	1
Small bowel adenocarcinoma (stage IV)	1
Testicular tumour (stage I) and oligoastrocytoma (WHO grade II)	1
Operations performed with curative intent	
Partial-thickness transanal local excision	1
Right orchidectomy and complete excision of oligoastrocytoma	1
Palliative surgery	
Small bowel resection and omentectomy	1

*Unless indicated otherwise; †values are median (range). JPS, juvenile polyposis syndrome; WHO, World Health Organization. No patient with a *BMPR1A* mutation was diagnosed with cancer.

had small bowel polyps in both the duodenum (0·2 cm) and jejunum (0·5 cm). One patient was diagnosed with a juvenile polyp located at the cricopharyngeus (1·1 cm).

Operations

The number of operations performed was comparable between patients with *BMPR1A* and *SMAD4* mutations (*Table 2*). Most patients underwent a restorative proctocolectomy or a subtotal/total colectomy to control colonic polyposis. In two patients with a *SMAD4* mutation a right colectomy and a transverse colectomy were performed for tubulovillous adenomas that could not be excised endoscopically. Total gastrectomy was carried out in seven patients with a *SMAD4* mutation, but no patient with a *BMPR1A* mutation. Indications for gastrectomy were chronic anaemia (3), severe polyposis (3) and dysplasia (1). One patient in the *BMPR1A* group underwent adhesiolysis and a small bowel resection 7 years after IPAA surgery owing to adhesive bowel disease.

Cancer phenotype

No patient with a *BMPR1A* mutation was diagnosed with cancer, but four men with a *SMAD4* mutation developed cancer (*Table 3*). Two parents were followed up at an outside clinic until the diagnosis of cancer, whereas the others were under surveillance in the authors' institution. The gastrointestinal cancer risk in patients with JPS and a *SMAD4* mutation was 11 per cent (3 of 27).

Discussion

Previous studies have shown that JPS carries a 50 per cent cumulative lifetime risk of developing colorectal and/or gastric cancer[11,14]. An association between colorectal cancer and *BMPR1A* mutation has been shown by the St Vincent's Hospital Group in Dublin[4] and others[15]. The present study did not confirm these findings, because patients had successful prophylaxis and surveillance; here, extracolonic cancers were found only in patients with a *SMAD4* mutation. This is in keeping with a generally more severe upper gastrointestinal polyp phenotype associated with a germline *SMAD4* but not with a germline *BMPR1A* mutation.

BMPR1A mediates the growth-suppressing TGF-β signal transduction pathway, a key intermediary of which is *SMAD4*[4,5,16]. The importance of *SMAD4* in preventing carcinogenesis was first suggested by Vogelstein and colleagues[17–19] in 1988; although there are some reports to the contrary[20], it is suggested that an allelic imbalance at the *SMAD4/DPC4* gene locus may play a key role in the progression of sporadic colorectal carcinoma[21]. It is not surprising, therefore, that adenomatous polyps can occur in patients with JPS[5,22,23], or that 8 per cent of polyps sent to pathology from patients with JPS are dysplastic[12]. There are no high-quality trials of polyp surveillance in JPS[24], but there are some reports of reduced incidence[25] and mortality[26] from colorectal cancer following polypectomy. The present data show equivalence of colorectal polyposis between the two major JPS genotypes.

As with familial adenomatous polyposis, the small intestine is at risk of cancer in JPS. Polyps and cancer can originate from the small bowel or ileal pouch in patients who have undergone gastrectomy or IPAA[27–29]. Complete small bowel imaging is not part of routine surveillance in JPS[12]. The authors generally reserve use of small bowel studies for patients who are symptomatic during surveillance. Although one patient with a *SMAD4* mutation developed a small bowel cancer in this series, this is not enough to make any comment about differences in small bowel cancer risk associated with genotype.

The main finding of the present study was the predominance of severe gastric polyposis in *SMAD4* mutation carriers. This translated into gastric cancer in two patients and a disproportionate incidence of gastrectomy among *SMAD4* mutation carriers. Considering the similar findings of previous studies[12] reporting increased risk of gastric polyposis and tendency for gastric cancer development in patients with JPS and *SMAD4* mutation, one implication of the present study is that upper gastrointestinal surveillance may be tailored according to genotype. This is already the case for HHT[7,12]. When indicated by profuse, uncontrollable or rapidly increasing polyposis, prophylactic or therapeutic total gastrectomy and total proctocolectomy may eliminate the risk of gastric and colorectal cancer. This is extreme, and it does not totally eliminate cancer risk.

Limitations of this study include its retrospective nature and small patient numbers. However, it has been shown that judicious surgery and effective surveillance can prevent colorectal cancer over a median follow-up of 11 years. This allows extracolonic cancers to develop; five such tumours are reported here, all of which were found in *SMAD4* mutation carriers who also had more severe gastric polyposis.

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References

1 Chow E, Macrae F. A review of juvenile polyposis syndrome. *J Gastroenterol Hepatol* 2005; **20**: 1634–1640.
2 Desai DC, Neale KF, Talbot IC, Hodgson SV, Phillips RK. Juvenile polyposis. *Br J Surg* 1995; **82**: 14–17.
3 Oncel M, Church JM, Remzi FH, Fazio VW. Colonic surgery in patients with juvenile polyposis syndrome: a case series. *Dis Colon Rectum* 2005; **48**: 49–56.
4 O'Riordan JM, O'Donoghue D, Green A, Keegan D, Hawkes LA, Payne SJ *et al.* Hereditary mixed polyposis syndrome due to a *BMPR1A* mutation. *Colorectal Dis* 2010; **12**: 570–573.
5 Jass JR. Colorectal polyposes: from phenotype to diagnosis. *Pathol Res Pract* 2008; **204**: 431–447.
6 Desai DC, Murday V, Phillips RK, Neale KF, Milla P, Hodgson SV. A survey of phenotypic features in juvenile polyposis. *J Med Genet* 1998; **35**: 476–481.
7 O'Malley M, LaGuardia L, Kalady MF, Parambil J, Heald B, Eng C *et al.* The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. *Dis Colon Rectum* 2012; **55**: 886–892.
8 Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S *et al.* A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in *MADH4* (*SMAD4*). *Lancet* 2004; **363**: 852–859.
9 Iyer NK, Burke CA, Leach BH, Parambil JG. *SMAD4* mutation and the combined syndrome of juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia. *Thorax* 2010; **65:** 745–746.
10 Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, Sistonen P *et al.* Mutations in the *SMAD4/DPC4* gene in juvenile polyposis. *Science* 1998; **280**: 1086–1088.
11 Coburn MC, Pricolo VE, DeLuca FG, Bland KI. Malignant potential in intestinal juvenile polyposis syndromes. *Ann Surg Oncol* 1995; **2**: 386–391.
12 Latchford AR, Neale K, Phillips RK, Clark SK. Juvenile polyposis syndrome: a study of genotype, phenotype, and long-term outcome. *Dis Colon Rectum* 2012; **55**: 1038–1043.
13 Brosens LA, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJ. Juvenile polyposis syndrome. *World J Gastroenterol* 2011; **17**: 4839–4844.
14 Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol* 1998; **5**: 751–756.
15 Ando T, Sugai T, Habano W, Jiao YF, Suzuki K. Analysis of *SMAD4/DPC4* gene alterations in multiploid colorectal carcinomas. *J Gastroenterol* 2005; **40**: 708–715.

16 Zhou XP, Woodford-Richens K, Lehtonen R, Kurose K, Aldred M, Hampel H *et al.* Germline mutations in *BMPR1A/ALK3* cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan–Riley–Ruvalcaba syndromes. *Am J Hum Genet* 2001; **69**: 704–711.
17 Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M *et al.* Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988; **319**: 525–532.
18 Thiagalingam S, Lengauer C, Leach FS, Schutte M, Hahn SA, Overhauser J *et al.* Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. *Nat Genet* 1996; **13**: 343–346.
19 Riggins GJ, Kinzler KW, Vogelstein B, Thiagalingam S. Frequency of *Smad* gene mutations in human cancers. *Cancer Res* 1997; **57**: 2578–2580.
20 Miyaki M, Kuroki T. Role of *Smad4* (*DPC4*) inactivation in human cancer. *Biochem Biophys Res Commun* 2003; **306**: 799–804.
21 Roth S, Laiho P, Salovaara R, Launonen V, Aaltonen LA. No *SMAD4* hypermethylation in colorectal cancer. *Br J Cancer* 2000; **83**: 1015–1019.
22 Brazowski E, Rozen P, Misonzhnick-Bedny F, Gitstein G. Characteristics of familial juvenile polyps expressing cyclooxygenase-2. *Am J Gastroenterol* 2005; **100**: 130–138.
23 Hood B, Bigler S, Bishop P, Liu H, Ahmad N, Renault M *et al.* Juvenile polyps and juvenile polyp syndromes in children: a clinical and endoscopic survey. *Clin Pediatr (Phila)* 2011; **50**: 910–915.
24 Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012; **143**: 844–857.
25 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977–1981.
26 Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687–696.
27 Ynson ML, Senatore F, Dasanu CA. What are the latest pharmacotherapy options for small bowel adenocarcinoma? *Expert Opin Pharmacother* 2014; **15**: 745–748.
28 Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. *Cancer Causes Control* 2005; **16**: 781–787.
29 Sene A, Thomas PE, Gautam V, Andrews NJ, McMahon RF, Taylor TV. Juvenile polyp in an ileoanal J pouch following restorative proctocolectomy for juvenile polyposis coli. *Br J Surg* 1989; **76**: 801.