Journal of Gastroenterology and Hepatology (2005) **20,** 1634–1640 DOI: 10.1111/j.1440-1746.2005.03865.x

REVIEW

Review of Juvenile Polyposis Syndrome

ELIZABETH CHOW AND FINLAY MACRAE

Department of Colorectal Medicine and Genetics, Royal Melbourne Hospital, Victoria, Australia

Abstract Juvenile Polyposis Syndrome is an uncommon hamartomatous disorder with significant gastrointestinal malignant potential. Mutations in SMAD4 and BMPR1A, implicated in the Transforming Growth Factor β pathway, have recently been characterized, and hold significance in the management of patients and at risk family members. This article reviews our knowledge to date of the genetics and clinicopathological features of the Juvenile Polyposis Syndrome, and discusses the current expert recommendations for genetic testing, disease screening and management.

Key words: BMPR1A, colorectal cancer, genetics, Juvenile Polyposis Syndrome, SMAD4.

INTRODUCTION

Juvenile Polyposis Syndrome is a clinically and genetically heterogeneous condition, a hamartomatous disorder first described in families in 1964.[1] This rare disease affects one in 100 000[2] to one in 160 000,[3] the wide variation reflects paucity of population-based data.[4] Both sporadic and familial cases with autosomal dominant inheritance are found. To date, there are no clinical, pathological, immunohistochemical or molecular markers that distinguish sporadic from the syndrome associated Juvenile Polyposis.[5] The Juvenile Polyposis Syndrome is regarded as distinct from solitary juvenile polyps which develop in 2% of children and adolescents, and have no malignant potential.

JUVENILE POLYPOSIS SYNDROME DIAGNOSIS AND CLINICAL FEATURES

Genetic syndromes including Juvenile Polyposis Syndrome, Cowden Syndrome (CS) and Bannayan Riley Ruvalcaba Syndrome (BRRS) all share the manifestations of intestinal juvenile polyps. Cowden Syndrome has additional pathognomonic features of mucocutaneous lesions (facial trichilemmoma, oral fibromas, acral keratosis) and associated tumors of the thyroid, breast and endometrium. Bannayan Riley Ruvalcaba Syndrome (BRRS) is characterized by mental retardation, macrocephaly, lipomatosis, hemangiomas and genital pigmentation.[6] In the absence of extra intestinal features consistent with Cowden Syndrome or Bannayan Riley Ruvalcaba Syndrome, the diagnosis of Juvenile Polyposis Syndrome is made when the following clinical criteria are met:[7]

- More than five juvenile polyps of the colon or rectum, or;
- Juvenile polyps in other parts of the gastrointestinal tract, or;
- Any number of juvenile polyps and a positive family history.

Sachatello *et al.*[8] further categorized Juvenile Polyposis patients into three phenotypic groups according to clinical presentation and disease course: (i) Juvenile Polyposis of infancy; (ii) Juvenile Polyposis Coli (colonic involvement only); and (iii) Generalized Juvenile Polyposis.

Juvenile Polyposis of infancy is the most severe form of the disease with poor prognosis. The entire gastrointestinal tract is involved. The disease is characterized by early presentation in infancy with gastrointestinal bleeding, intussusception, rectal prolapse, or protein losing enteropathy. Other associated features include macrocephaly, digital clubbing and hypotonia. No family history is found.[9]

Both Generalized Juvenile Polyposis and Juvenile Polyposis of the Colon may present with acute or chronic gastrointestinal bleeding, anaemia, prolapsed rectal polyps, abdominal pain and diarrhoea.[10] Long-term studies suggest that symptoms or anaemia usually

Correspondence: Dr Elizabeth Chow, Familial Cancer Clinic, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia. Email: Elizabeth.Chow@mh.org.au
Accepted for publication 9 November 2004.

manifest before progressing to malignancy.[11] Among 10 Jewish Familial Juvenile Polyposis pedigrees at the Tel Aviv Medical Center, serious clinical manifestations with bowel obstruction occurred in 17% (6 individuals), and gastrointestinal bleeding was reported in 71% (25 individuals).[12] Coburn *et al.*[13] found in a study of 218 patients that Juvenile Polyposis Coli patients present at ages between 5–15, whereas Generalized Juvenile Polyposis patients present at a younger age.

Hofting *et al.*[14] reviewed 272 Juvenile Polyposis Syndrome patients to show affected sites in order of frequency to be colorectum (98%), stomach (14%), jejunum and ileum (7%) and duodenum (2%).

The mechanism of inheritance is autosomal dominant with variable penetrance. Twenty to 50% of cases have a family history of Juvenile Polyposis Syndrome. The age related penetrance of the disease is still to be elucidated by further studies; however, evidence suggests that there is low probability of developing juvenile polyposis after age 45.[11] Indeed the mean age of diagnosis of familial Juvenile Polyposis among 10 Jewish pedigrees at the Tel Aviv Medical Center was 26.1 years ± 15.6 (SD).[12] Genetic anticipation had been reported in the Juvenile Polyposis Syndrome, implying that age of presentation becomes younger with each generation. This could be explained in part by increased awareness and surveillance for younger generations.[15] Associated congenital birth defects are found in 15% of cases, usually in those with no family history, and include malrotation of the midgut, cardiac and cranial abnormalities, cleft palate, polydactyly and genitourinary defects.[9]

HISTOPATHOLOGY

Patients with the Juvenile Polyposis Syndrome often have 50–200 polyps distributed throughout the colon, although some patients may have polyps in stomach and small intestine. The polyps range from a few millimeters to a few centimeters in size. The intervening mucosa between polyps is normal in contrast to Familial Adenomatous Polyposis.

Macroscopically, a juvenile polyp has a smooth, spherical red head on a narrow stalk. (Fig. 1). Microscopic changes are mucin-filled cystic dilatation of the epithelial tubules embedded in abundant lamina propria. The tubules are lined by normal columnar epithelium. The cellular infiltrate of the lamina propria includes myofibroblasts, fibroblasts, and macrophages. Muscularis mucosa is not included within the stroma.[9]

MALIGNANCY IN JUVENILE POLYPOSIS

The malignant potential of a solitary juvenile polyp is low, and patients with solitary juvenile polyps do not require close surveillance. One published study showed that 82 patients with solitary juvenile polyps followed for 10–25 years had no increased relative risk of colorectal carcinoma or death compared with the general population.[16] In contrast, Juvenile Polyposis Syndrome has significant malignant potential, but unlike the other hamartomatous condition, Peutz Jeghers Syndrome, extra-intestinal cancers are not prominent.

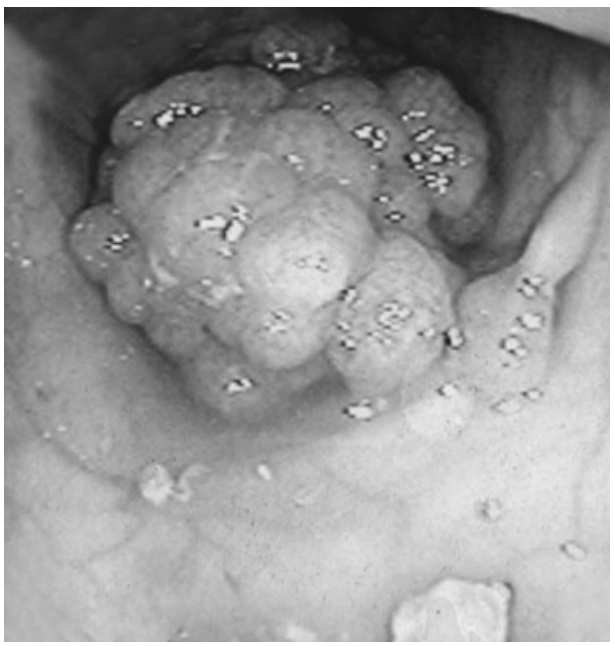

Figure 1 Typical appearance of Juvenile Polyps at colonoscopy.

A large series by Howe *et al.*[15] in 1998 showed that in 117 related people, 16 of 29 affected patients developed gastrointestinal cancer. Eleven had colon cancer, four stomach cancers, one pancreatic cancer, and one patient was reported to have cancer of the ampulla/duodenum. Rozen *et al.*[12] showed that among 10 Jewish pedigrees with familial Juvenile Polyposis, gastrointestinal cancers occurred in eight patients (22.9%): six were colonic cancers, and two were gastric cancers.

In 1999, Agnifili *et al.*[17] performed a literature review of 51 reports from 12 countries with a total of 271 Juvenile Polyposis patients. The overall incidence of adenomas was 18.45% (50 patients), carcinomas was 17.34% (43 patients), with even distribution between the sexes. In the group of 50 patients with adenomatous changes, 48 were colorectal adenomas, one was gastric adenoma, and one was duodenal adenoma. Similarly, in the group of 47 patients with carcinoma, the findings were not limited to the colorectum, with two gastric cancers, two duodenal and pancreatic cancers and two jejunal cancers. The risk of neoplasia was higher in the Generalized Juvenile Polyposis patients (21 of 32 patients i.e. 65.94%) compared with Juvenile Polyposis Coli (73 of 202 patients i.e. 36.14%). In 118 familial Juvenile Polyposis patients, 56 (47.38%) had neoplasia (28 adenomas, 28 carcinomas), while 40 of 62 sporadic Juvenile Polyposis patients (i.e. no family history) (64.51%) were found to have adenomas (23) or cancer (17). The risk of malignancy commences from the age of 20 years and increases in the 30s. There is no direct

evidence to suggest correlation between earlier onset of Juvenile Polyposis Syndrome and greater or earlier neoplastic presentation. The St Mark's Polyposis Registry data showed that the cumulative risk of cancer (among patients who had no cancer at time of initial referral to the registry) was 68% by 60 years of age.[9]

GENETICS OF JUVENILE POLYPOSIS

Juvenile Polyposis Syndrome is an autosomal dominant condition with incomplete penetrance. Research in Juvenile Polyposis Syndrome families has identified two specific gene changes causing disruption of the transforming growth factor β (TGF β) signal transduction pathway: SMAD4 and BMPR1A. Each germline mutation has a prevalence of 20%;[10] however, undefined genetic heterogeneity still remains in 60% of patients with Juvenile Polyposis Syndrome. Two laboratories offering clinical genetic testing for Juvenile Polyposis Syndrome are the Molecular Pathology Laboratory, Ohio State University and the Institute of Human Genetics, University of Bonn, Germany. In addition, three laboratories offer research genetic testing: the Marchuk Laboratory, Duke University Medical Center, Durham, North Carolina; the Howe Research Laboratory, University of Iowa College of Medicine, Iowa City and the Molecular and Population Genetics Laboratory, Cancer Research UK, London.

SMAD4 gene

Somatic mutations in SMAD4 (also known as MADH4 and DPC4) located on chromosome 18q21.1 have been found to be in up to 50% of pancreatic tumors[18,19] and 15% of colorectal tumors.[20]

SMAD4 germline mutations were first identified through linkage analysis in five of nine Juvenile Polyposis patients in 1998.[21] By 2004, of the combined total of 141 patients tested for SMAD4 mutations in six studies (Friedl *et al.*[22] Woodford-Richens *et al.*,[6] Howe *et al.*,[21,23] Roth *et al.*,[24] Kim *et al.*,[25]) 32 patients (22.7%) have been found to be mutation positive for SMAD4.[23] A total of 26 different SMAD4 mutations have been found, consisting of 15 deletions, two insertions and 15 substitutions (5 nonsense, 10 missense).[23] The most common mutation in SMAD4 is a 4 base deletion in exon 9, which is therefore a mutational hotspot.[26] Mutation detection rates in sporadic and familial studies yield results between 5% and 60%. The inter study differences may be due to varied clinical and histopathological patient selection criteria.[27]

SMAD4 encodes a cytoplasmic mediator involved in the TGF β signal transduction pathway, which mediates growth inhibitory signals from the cell surface to the nucleus. Upon activation by TGF β or related ligands, serine and threonine kinase receptors phosphorylate proteins of the SMAD family, which then form heteromeric complexes with SMAD4. These complexes are transported into the nucleus and interact with cellular DNA to cause apoptotic and growth inhibition responses. Mutations in the SMAD4 gene map to the COOH terminus, which is important in formation of the heterometric complex. The loss of growth inhibition results in neoplastic progression.[21] Other SMAD family member mutations (SMAD1, SMAD2, SMAD3, SMAD5 and SMAD7) have been tested to be negative in Juvenile Polyposis patients, despite being good candidate genes for mutation as they are involved in the TGF β signaling pathway.[24,28]

The mechanism of invasive epithelial malignancy in Juvenile Polyposis is not well understood. In 1997, Jacoby[29] found clonal genetic alterations in the lamina propria rather than epithelial elements. The *Landscaper defects* hypothesis was generated by Kinzler and Vogelstein[30] to explain how stromal overgrowth in juvenile polyps can predispose to epithelial malignancy. Factors secreted by the proliferative stroma create an abnormal stromal microenvironment which influences or 'landscapes' the adjacent epithelial cells, and the resulting regeneration of damaged epithelium can lead to dysplasia and neoplasia. However, this theory has been disputed by the findings of Woodford Richens *et al.*[31] This group found loss of the wild type allele at the SMAD4 locus of 18q in polyps of patients who had germline SMAD4 mutation. Thus, SMAD4 behaves in a classic tumor suppressor fashion in Juvenile Polyposis, where the somatic loss of the wild type allele is the first somatic mutation leading to hamartomatous polyp formation. Variable regions of the chromosome lost in different polyps may indicate different mechanisms involved in the inactivation of the second copy of SMAD4. Using the Florescence In Situ Hybridization technique, biallelic inactivation of SMAD4 was found in both epithelial cells and some stromal cells (stromal fibroblasts and pericryptal myofibroblasts). This may indicate a common clonal origin for epithelium and part of the stroma of a juvenile polyp. Woodford-Richens *et al.*[31] also propose that epithelial malignancies in Juvenile Polyposis Syndromes are likely to develop through direct progression in the epithelial cells and that SMAD4 acts as a gatekeeper type of tumor suppressor in the epithelium of both Juvenile Polyposis Syndrome and sporadic cancers.

Woodford Richens *et al.*[32] suggest in a subsequent study that SMAD4 mutation carriers' polyps have less prominent stroma and a more prominent epithelial component than those patients without SMAD4 mutations. This may give SMAD4 mutation carriers a higher risk of cancer compared to those without SMAD4 mutations. However, polyp morphology cannot be relied upon to suggest the likelihood of a germline SMAD4 mutation.

BMPR1A gene

BMPR1A (bone morphogenic protein receptor 1 A, also known as ALK3) is a gene upstream from SMAD4 in the TGF-β pathway which has also been found responsible for a subset of Juvenile Polyposis cases. The BMPR1A gene encodes for a type I serine/threonine kinase receptor that belongs to the TGF β receptor

SMAD super-family. When BMPR1A is activated through phosphorylation, it phosphorylates the SMAD family, forming complexes that migrate into the nucleus, associate with DNA binding proteins and regulate the transcription of DNA sequences. Mutations in BMPR1A encode BMP receptors that lack the intracellular serine-threonine kinase domain and result in loss of (BMP) intracellular signaling through SMAD4. Other BMP receptor genes (BMPR1B, BMPR2) were found not to contribute to Juvenile Polyposis Syndrome in a study of 32 SMAD4 or BMPR1A mutation negative cases by Howe *et al.*[23] Similarly, another candidate gene ACVR1, a Type 1 activin receptor within the TGFB super-family, was found to be-non-contributary.[23]

Nonsense mutations in BMPR1A on chromosome 10q22-23 were first identified in 2001 through genome-wide screening in four of four North American Juvenile Polyposis family groups.[33] Zhou *et al.*[34] reported 10 (40%) BMPR1A mutations in 25 European families. Friedl *et al.*[22] found five BMPR1A mutations among 29 European Juvenile Polyposis cases. The largest series from Howe *et al.*[23] found 16 BMPR1A mutation positive cases among 77 patients from United States, Canada, South America and Europe (20.8%). There has been one case of BMPR1A gene mutation reported in a cohort of four Korean Juvenile Polyposis patients.[35] Rozen *et al.*[12] found two out of 10 Jewish pedigrees positive for BMPR1A gene mutation. Thirty-one different BMPR1A mutations have been detected: there are nine deletions, one insertion, two splice site mutations and 19 substitutions (10 missense, 9 nonsense).[23]

Genotype phenotype correlation

Sayed *et al.*[4] studied 54 familial and sporadic Juvenile Polyposis cases for characteristics that exist between patients with and without mutations. Twenty-two cases (41%) were positive for either SMAD4 or BMPR1A (MUT+); nine patients (16.7%) were positive for SMAD4 mutations and 13 (24%) cases were BMPR1A positive. Thirty-two patients (59%) were mutation negative (MUT-).

The frequency of a family history of gastrointestinal cancer was significantly higher for MUT+ group (89%) compared to MUT– group (52%). A trend to older age of diagnosis, a higher frequency of familial cases and >10 colonic polyps was observed in the MUT+ group compared with MUT– group, without reaching statistical significance.

There were no statistically significant differences in clinical factors between BMPR1A+ and MUT– groups. Statistically significant differences between SMAD4+ and MUT– groups were: SMAD4+ group had a later age of diagnosis (16.5 years *vs* 9.2 years), a higher frequency of positive family history of gastrointestinal cancer (89% *vs* 52%) and a higher frequency of upper gastrointestinal polyps (86% *vs* 23%). The only statistically significant difference between SMAD4 and BMPR1A+ patients was a higher prevalence of family history of upper gastrointestinal polyps: 86% versus 10%.

SMAD4+ cases have a higher frequency of upper gastrointestinal polyps compared with MUT– cases, and a higher prevalence of family members with upper gastrointestinal polyps compared with BMPR1A and MUT– cases. Further evidence of this genotype-phenotype correlation was reported by Friedl *et al.*[22] in 2002 in which massive gastric polyposis was a feature in SMAD4 gene mutation carriers, but not in BMPR1A gene positive or mutation negative patients. A total of 29 Juvenile Polyposis patients were studied: four of the seven SMAD4 gene mutation carriers presented with massive gastric polyposis, some requiring partial or total gastrectomy, and one of these patients had four relatives with massive gastric polyposis or gastric cancer. In comparison, none of the five BMPR1A positive patients or the mutation-negative patients had such presentations. This finding has also been supported by the high prevalence of upper gastrointestinal involvement in 11 of 29 affected members of a large Iowa family group with SMAD4 mutation.[21,36]

SMAD4 gene mutations appear to predispose to Generalized Juvenile Polyposis Syndrome with a higher prevalence of upper gastrointestinal polyposis, which is associated with more severe symptoms such as blood loss and iron deficiency anaemia.[37] It is therefore postulated that SMAD4+ cases may have more severe clinical manifestations and may need closer monitoring with upper endoscopy for development of polyps and cancer. A small proportion of BMPR1A and MUT– cases still has family history of upper gastrointestinal polyps, so upper gastrointestinal screening is still needed but at longer intervals (e.g. 5 yearly *vs* every 1–3 years for SMAD4+ patients[4]) (Table 2). Further characterization of gene expression is required to substantiate these findings, which holds implications for the clinical and genetic screening of Juvenile Polyposis patients.

PTEN gene

Juvenile Polyps occur with syndrome-specific features in other diseases such as Cowden, Bannayan-Ruvalcaba-Riley and Gorlin Syndromes with developmental abnormalities, dysmorphic features or other tumors. Mutations in the PTEN gene (10q23.3) have been shown to cause Cowden and Bannayan-Ruvalcaba-Riley Syndromes whereas PTCH (9q31) mutations cause Gorlin Syndrome. Although one study has shown PTEN mutation in Juvenile Polyposis families, it is possible that the original family group studied may actually have Cowden's Syndrome.[38] Mutations in PTEN and PTCH have been excluded as causative genes in almost all Juvenile Polyposis patients and are only considered in the context of Juvenile Polyposis with clinical features of Cowden, Bannayan-Ruvalcaba-Riley or Gorlin Syndromes.[6]

MANAGEMENT OF JUVENILE POLYPOSIS

Current guidelines for patients and their at-risk family members are based on expert opinion rather than sci-

entific proof, due to the lack of case-controlled studies. There are no known dietary or drug prevention strategies for Juvenile Polyposis Syndrome.

Management of the proband with juvenile polyposis

Genetic testing

Recent discoveries of SMAD4 and BMPR1A gene mutations in Juvenile Polyposis mean that now a proband can be tested for such mutations. Genetic counseling should be conducted prior genetic testing with particular attention to the family pedigree, providing specific information about clinical manifestations of Juvenile Polyposis Syndrome, risk of gastrointestinal cancer and surveillance recommendations. The patient must be informed of the risks, benefits and limitations of the tests and be counseled about the implications of positive/negative test result for the future care both of the patient and the at-risk family members.

Lower gastrointestinal surveillance

Refer to Table 1 for expert opinions regarding lower gastrointestinal surveillance strategies.

Upper gastrointestinal surveillance

Enteroscopy is the preferred upper gastrointestinal tract surveillance modality to detect polyps well into the jejunum. Small bowel follow through and capsule endoscopy are also valuable. Refer to Table 2 for expert recommendations regarding frequency of upper gastrointestinal surveillance.

Table 1 Lower gastrointestinal surveillance strategies

Recommendations by Howe *et al.*[11]	Recommendations by Dunlop[40]
From age 15 or earlier if symptoms:	From age 15–18 or earlier if symptoms
Do full blood examination and endoscopy	Intervals 1–2 years
If normal, repeat 3 yearly	Gene carriers or affected continue surveillance until age 70
If polyps are found, remove and screen annually until polyp free, then 3 yearly	

Colonic juvenile polyps

A patient who has only a few uncomplicated polyps should be managed with endoscopic polypectomy. Efforts should be made to clear the colon by colonoscopy. If a juvenile polyp shows high grade dysplasia and the polyp cannot be completely removed endoscopically, or if invasive adenocarcinoma cancer is detected, then consideration should be given to colectomy. In those patients with large numbers of juvenile polyps, especially those with significant anaemia or hypoproteinemia, subtotal colectomy with ileorectal anastomosis is recommended, or proctocolectomy with J pouch ileo-anal anastomosis.[11] Subsequent systematic colorectal and/or pouch surveillance are necessary to allow timely detection of recurrent gastrointestinal neoplasia.

Upper gastrointestinal polyps

A few gastric polyps warrant endoscopic polypectomy, but in multiple or diffuse gastric polyposis, subtotal or total gastrectomy may be necessary. Duodenal or small bowel polyposis may need removal surgically.

Management of at-risk family members

Genetic testing

If a specific gene mutation such as SMAD4 or BMPR1A has been detected in a proband, then presymptomatic genetic testing can be offered to at-risk family members to determine future surveillance strategies in order to allow for early diagnosis and treatment of juvenile polyps.

Clinical management

(i) Asymptomatic SMAD4 or BMPR1A mutation carriers and at-risk family members of probands with no mutation detected: The same surveillance strategy is recommended as for probands, refer to Tables 1 and 2.

(ii) If a specific mutation has been detected in the proband, and the at-risk family members have tested negative for specific mutation: Howe *et al.*[11] recommend confirmation of the negative phenotype with

Table 2 Upper gastrointestinal surveillance strategies

Recommendation by Howe *et al.*[11]	Recommendation by Dunlop[40]	Recommendation by Sayed *et al.*[4]
Contemporaneously with colonoscopy	From age 25	Frequency: SMAD4+ patients: 1–3 yearly
Biliary and/or pancreatic duct brushings recommended if elevated amylase or abnormal liver function tests	Frequency: 1–2 yearly contemporaneously with colonoscopy	Mutation negative or BMPR1A+ patients: 5 yearly

baseline screening consisting of complete full blood examination, upper and lower endoscopy in adolescence. If symptoms develop (e.g. rectal bleeding, rectal prolapse or abdominal pain) or if anaemia is detected on full blood examination, endoscopy will be necessary. If asymptomatic, future upper and lower endoscopy should be performed every 10 years until 45 years of age. After age 45, standard guidelines for colorectal cancer screening in the general population should be followed. However, other experts argue for more frequent screening than every 10 years given the genetic heterogeneity of the Juvenile Polyposis Syndrome.[39]

Compliance issues

To date, only one study by Rozen *et al.*[12] has explored the issue of compliance for evaluation and follow up. Among 10 Jewish Juvenile Polyposis pedigrees at the Tel Aviv Medical Center, overall pedigree compliance was inadequate in 20%, while overall individual compliance was inadequate in 26%. The reasons for poor compliance include lack of knowledge in the families and the general medical community, lack of financial support from health insurance companies, cultural issues surrounding the stigma associated with genetic disease and lack of psychosocial support in the family and medical services. While some of these issues are unique to the orthodox Jewish and Arabic community, others are common experiences warranting attention to genetic counseling, wider education of both the medical community and the population at large.

CONCLUSION

Juvenile Polyposis Syndrome can present with anaemia, rectal bleeding, and particularly in the pediatric population disastrous complications of bowel infarction due to intussusception. It also has significant gastrointestinal malignancy potential. The new genetic knowledge regarding SMAD4 and BMPR1A genes allows for genotypic diagnosis in 40–50% of patients with Juvenile Polyposis Syndrome. Europeans are the predominant group studied in the literature, however, there may be non-Caucasian founder mutations. Two published studies of Korean patients revealed mutation carriers of the SMAD4 or BMPR1A genes.[25,35] However, in our local experience enriched with a South Mediterranean and East/South-east Asian population, we are unaware of non-Caucasian Juvenile Polyposis Syndrome patients. In families with an identified mutation, genetic testing informs surveillance planning in gene carriers, allowing for early detection and management of polyps and malignancies, as well as increased awareness, and improved clinical outcome with respect to complications of bowel infarction and intussusception. Further work will be required to fully characterize the gene expression in this clinically and genetically heterogeneous syndrome.

ACKNOWLEDGMENTS

Dr Elizabeth Chow is supported by Hicks Foundation Scholarship and Edith Viola Reid Scholarship, Faculty of Medicine, University of Melbourne.

REFERENCES

1 McColl IBH, Veale AM, Morson BC. Juvenile Polyposis Coli. *Proc. R. Soc. Med.* 1964; **57**: 896–7.
2 Burt RW, Bishop DT, Lynch HT, Rozen P, Winawer SJ. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the prevention of colorectal cancer. *Bull. World Health Organ.* 1990; **68**: 655–65.
3 Chevrel J-PAJ, Gueraud J-P. Trois cas familiaux de polypose juvenile. *Chirurgie* 1975; **101**: 708–21.
4 Sayed MG, Ahmed AF, Ringold JR *et al.* Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. *Ann. Surg. Oncol.* 2002; **9**: 901–6.
5 Fogt F, Brown C, Badizadegan K, Zimmerman R, Odze R. Low prevalence of loss of heterozygosity and SMAD4 mutations in sporadic and familial Juvenile Polyposis Syndrome-associated Juvenile Polyps. *Am. J. Gastroenterol.* 2004; **99**: 2025–31.
6 Woodford-Richens K, Bevan S, Churchman M *et al.* Analysis of genetic and phenotypic heterogeneity in juvenile polyposis. *Gut* 2000; **46**: 656–60.
7 Jass JR, Williams CB, Bussey HJ, Morson BC. Juvenile polyposis—a precancerous condition. *Histopathology* 1988; **13**: 619–30.
8 Sachatello CR, Hahn IS, Carrington CB. Juvenile gastrointestinal polyposis in a female infant: report of a case and review of the literature of a recently recognized syndrome. *Surgery* 1974; **75**: 107–14.
9 Jass JR. Juvenile POlyposis. In: Phillips RTJ, Spiegelman A, eds. *Familial Adenomatous Polyposis and Other Polyposis Syndromes.* 1st edn. London: Edward Arnold, 1994; 203–14.
10 Merg A, Howe JR. Genetic conditions associated with intestinal juvenile polyps. *Am. J. Med. Genet.* 2004; **129C**: 44–55.
11 Howe JR, Ringold JC, Hughes JH, Summers RW. Direct genetic testing for Smad4 mutations in patients at risk for juvenile polyposis. *Surgery* 1999; **126**: 162–70.
12 Rozen P, Samuel Z, Brazowski E, Jakubowicz M, Rattan J, Halpern Z. An audit of familial juvenile polyposis at the Tel Aviv Medical Center: demographic, genetic and clinical features. *Familial Cancer* 2003; **2**: 1–7.
13 Coburn MCPV, DeLuca FG, Bland KI. Malignant potential in intestinal juvenile polyposis syndromes. *Ann. Surg. Oncol.* 1995; **2**: 386–91.
14 Hofting I, Pott G, Stolte M. [The syndrome of juvenile polyposis]. *Leber Magen Darm* 1993; **23**: 111–12.
15 Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann. Surg. Oncol.* 1998; **5**: 751–6.
16 Nugent KP, Talbot IC, Hodgson SV, Phillips RK. Solitary juvenile polyps: not a marker for subsequent malignancy. *Gastroenterology* 1993; **105**: 698–700.
17 Agnifili A, Verzaro R, Gola P *et al.* Juvenile polyposis: case report and assessment of the neoplastic risk in 271

patients reported in the literature. *Dig. Surg.* 1999; **16**: 161–6.
18 Hahn SA, Schutte M, Hoque AT *et al.* DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science* 1996; **271**: 350–3.
19 Schutte M, Hruban RH, Hedrick L *et al.* DPC4 gene in various tumor types. *Cancer Res.* 1996; **56**: 2527–30.
20 Thiagalingam S, Lengauer C, Leach FS *et al.* Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. *Nat. Genet.* 1996; **13**: 343–6.
21 Howe JR, Roth S, Ringold JC *et al.* Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science* 1998; **280**: 1086–8.
22 Friedl W, Uhlhaas S, Schulmann K *et al.* Juvenile polyposis: massive gastric polyposis is more common in MADH4 mutation carriers than in BMPR1A mutation carriers. *Hum. Genet.* 2002; **111**: 108–11.
23 Howe JRSM, Ahmed AF, Ringold J *et al.* The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. *J. Med. Genet.* 2004; **41**: 484–91.
24 Roth S, Sistonen P, Salovaara R *et al.* SMAD genes in juvenile polyposis. *Genes Chromosomes Cancer* 1999; **26**: 54–61.
25 Kim IJKJ, Yoon KA, Heo SC *et al.* Germline mutations of the dpc4 gene in Korean juvenile polyposis patients. *Int. J. Cancer* 2000; **86**: 529–32.
26 Howe JR, Shellnut J, Wagner B *et al.* Common deletion of SMAD4 in juvenile polyposis is a mutational hotspot. *Am. J. Hum Genet* 2002; **70**: 1357–62.
27 Burger B, Uhlhaas S, Mangold E *et al.* Novel de novo mutation of MADH4/SMAD4 in a patient with juvenile polyposis. *Am. J. Med. Genet.* 2002; **110**: 289–91.
28 Bevan S, Woodford-Richens K, Rozen P *et al.* Screening SMAD1, SMAD2, SMAD3, and SMAD5 for germline mutations in juvenile polyposis syndrome. *Gut* 1999; **45**: 406–8.
29 Jacoby RF, Schlack S, Cole CE, Skarbek M, Harris C, Meisner LF. A juvenile polyposis tumor suppressor locus at 10q22 is deleted from nonepithelial cells in the lamina propria. *Gastroenterology* 1997; **112**: 1398–403.
30 Kinzler KW, Vogelstein B. Landscaping the cancer terrain. *Science* 1998; **280**: 1036–7.
31 Woodford-Richens K, Williamson J, Bevan S *et al.* Allelic loss at SMAD4 in polyps from juvenile polyposis patients and use of fluorescence in situ hybridization to demonstrate clonal origin of the epithelium. *Cancer Res.* 2000; **60**: 2477–82.
32 Woodford-Richens KL, Rowan AJ, Poulsom R *et al.* Comprehensive analysis of SMAD4 mutations and protein expression in juvenile polyposis: evidence for a distinct genetic pathway and polyp morphology in SMAD4 mutation carriers. *Am. J. Pathol* 2001; **159**: 1293–300.
33 Howe JR, Bair JL, Sayed MG *et al.* Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. *Nat. Genet.* 2001; **28**: 184–7.
34 Zhou XP, Woodford-Richens K, Lehtonen R *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**: 704–11.
35 Kim IJPJ, Kang HC, Kim KH *et al.* Identification of a novel BMPR1A germline mutation in a Korean juvenile polyposis patient without SMAD4 mutation. *Clin. Genet.* 2003; **63**: 126–30.
36 Howe JR, Ringold JC, Summers RW, Mitros FA, Nishimura DY, Stone EM. A gene for familial juvenile polyposis maps to chromosome 18q21.1. *Am. J. Hum. Genet.* 1998; **62**: 1129–36.
37 Bussey H. *Precancerous Lesions of the Gastrointestinal Tract*. New York: Raven Press, 1983.
38 Olschwang S, Serova-Sinilnikova OM, Lenoir GM, Thomas G. PTEN germ-line mutations in juvenile polyposis coli. *Nat. Genet.* 1998; **18**: 12–14.
39 Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. *Ann. Surg. Oncol.* 2001; **8**: 319–27.
40 Dunlop MG. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polypolis, juvenile polyposis, and Peutz-Jeghers syndrome. *Gut* 2002; **51** (Suppl. 5): V21–7.