Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Cancer Prone Disease Section

Short Communication

Familial Juvenile Polyposis Syndrome

Scott K Sherman, James R Howe

University of Iowa Department of Surgery, Iowa City, IA, USA (SKS, JRH)

Published in Atlas Database: May 2013

Online updated version : http://AtlasGeneticsOncology.org/Kprones/FamJuvPolID10047.html
DOI: 10.4267/2042/51821

Identity

Other names
JPS

Inheritance
Autosomal Dominant.

Clinics

Phenotype and clinics

Juvenile Polyposis Syndrome (JPS) is a heritable syndrome characterized by multiple juvenile polyps, which occur mainly in the colorectum, but can also occur in the stomach and throughout the gastrointestinal tract.

The incidence of Juvenile Polyposis is around 1 in 100000 and although many Juvenile Polyposis patients are diagnosed in childhood, the word "juvenile" in the syndrome's name refers not to the age of the patient, but rather to the histologic classification of the polyp (as opposed to an adenomatous polyp, for example).

Juvenile Polyposis may be more common in patients of northern European ancestry, but the syndrome has been recognized throughout the world in patients of many ethnicities.

The presenting symptom of Juvenile Polyposis is most often passage of blood per rectum, with subsequent endoscopic evaluation revealing the presence of multiple polyps.

Solitary juvenile polyps can be a normal finding on colonoscopy in a young patient, but multiple polyps are unusual and are often indicative of JPS. Juvenile Polyposis Syndrome is distinguished by a large number of polyps, recurrent polyps, or a family history of juvenile polyps. Current diagnostic criteria include the presence of five or more juvenile polyps in the colorectum, or at least one upper and one lower GI juvenile polyp, or any number of juvenile polyps in a patient with a family history of Juvenile Polyposis.

Juvenile Polyposis has variable expressivity. Even within the same family carrying a particular susceptibility mutation, some patients may develop polyps at a young age, while others may have negative endoscopic screening for many years before manifesting polyposis symptoms. The number of polyps that occur is also highly variable and ranges from several to hundreds.

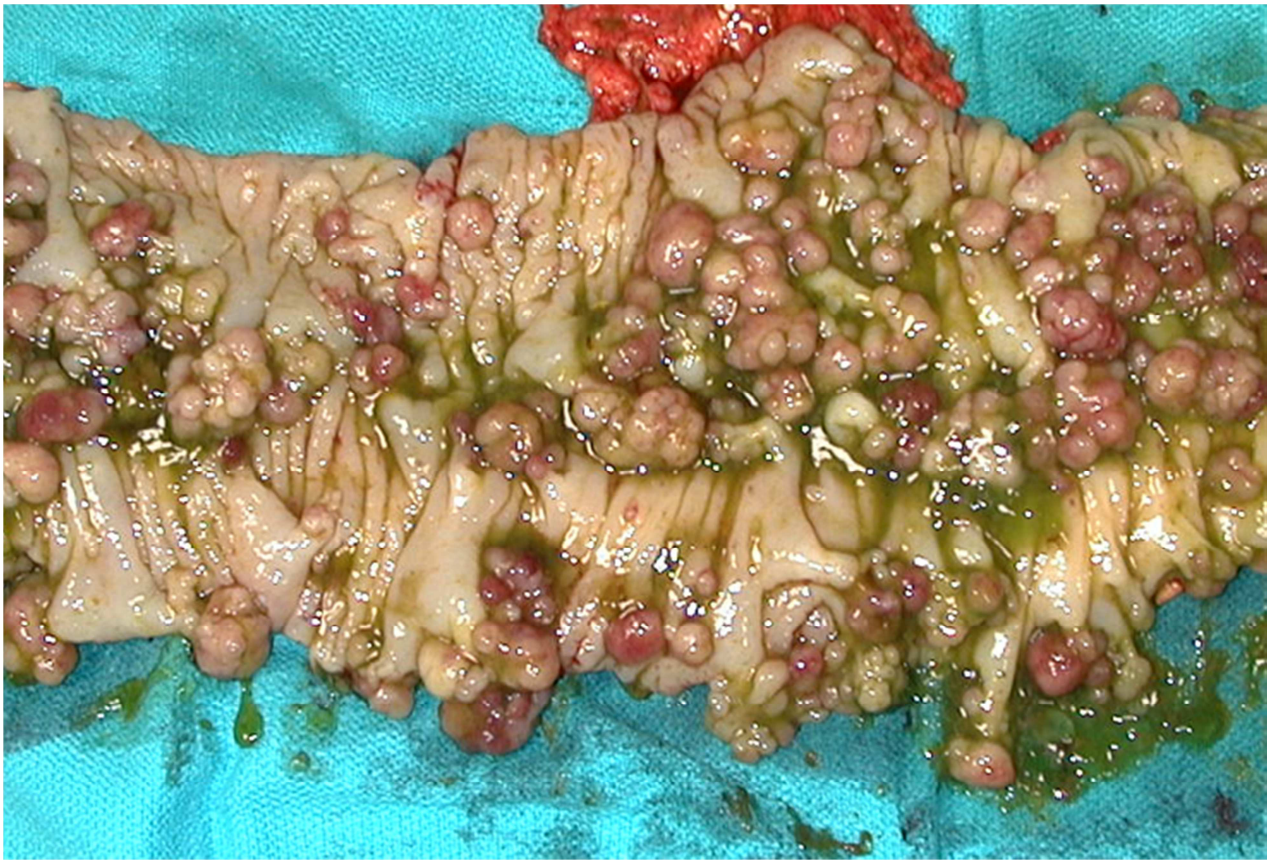
In addition to polyps, approximately 15% of patients may have congenital anomalies, particularly of the heart or aorta.

Differential Diagnosis

Juvenile Polyposis must be distinguished from hamartomatous polyps found in Peutz-Jegher's, Cowden's, Gorlin's, and Bannayan-Riley-Ruvalcaba syndromes.

These syndromes are caused by mutations in different genes (STK11 for Peutz-Jegher's, PTEN for Cowden's and Bannayan-Riley-Ruvalcaba and PTCH1 for Gorlin's), and have additional features which are not seen in JPS.

Due to a genetic defect in the same gene (SMAD4), some patients with Juvenile Polyposis Syndrome also show features of Hereditary Hemorrhagic Telangiectasia, and patients with a large continuous deletion of both BMPR1A and PTEN manifest severe Juvenile Polyposis Syndrome of Infancy, which is associated with additional severe malformations.



Diffuse polyposis is evident in this colectomy specimen of a Juvenile Polyposis Syndrome patient.

Neoplastic risk

Unlike the pre-malignant adenomatous polyps of APC or HNPCC syndromes, Juvenile Polyps are considered benign. Nevertheless, JPS patients do have an increased lifetime risk for colon cancer that is estimated to be as high as 50%.

JPS patients also have an increased risk of gastric cancer, which may be highest in patients with SMAD4 mutations.

The finding of an isolated juvenile polyp in a patient without evidence of Juvenile Polyposis Syndrome is not associated with an increased risk of cancer.

Treatment

Due to the increased risk of cancer, close screening of affected patients and their family members is warranted.

Once a patient is diagnosed with JPS, he or she should undergo genetic testing.

If positive, their family members should be tested also to determine who requires screening. However, because only around 50% of patients carry a known mutation, if no known mutation is identified, all family members must be considered to be at-risk and offered screening.

Upper and lower endoscopies should be performed at diagnosis and all polyps removed.

Endoscopy should then be performed annually, until no polyps are found, after which time endoscopy may be performed every three years.

In cases where removal of all polyps is not feasible due to diffuse polyposis, or when evidence of dysplasia is present, colectomy or gastrectomy should be offered. Colectomy or gastrectomy is also

indicated when polyps result in intractable bleeding, uncontrollable protein loss through heavy mucus production, recurrent intussusception, or severe and persistent symptoms of pain, nausea, or diarrhea.

Genes involved and proteins

Note

Two genes, SMAD4 and BMPR1A, have been confirmed to cause Juvenile Polyposis Syndrome. Together, these account for approximately 50% of cases. Both are members of the BMP/TGF-Beta signaling pathway.

SMAD4

Location

18q21.1

Protein

Note

SMAD4 is a 436 amino-acid signal transduction

peptide containing an N-terminal MH1 domain and a c-terminal MH2 domain.
SMAD4 is localized to the cytoplasm, but translocates to the nucleus once bound by activated R-Smad proteins, such as SMAD2 and SMAD3 (which are activated by TGF-β receptors) and SMAD1, SMAD5, SMAD8 (activated by BMP receptors).
In the nucleus, SMAD4 interacts with additional proteins to stimulate gene transcription. At least 14 distinct germ line SMAD4 missense, nonsense, deletion, and promoter mutations lead to JPS.
Most mutations are concentrated towards the c-terminus of the SMAD4 protein.

BMPR1A

Location
10q22.3

Protein

Note
BMPR1A is a 532 amino-acid transmembrane serine/threonine kinase receptor activated by TGF-β superfamily ligands. As a transmembrane receptor, BMPR1A is normally localized to the cell surface, but some JPS mutations may interfere with this localization. When activated by ligand binding, the BMPR1A receptor causes SMAD1,5, and 8 phosphorylation. The activated R-Smad complex can then bind SMAD4, stimulating its translocation to the nucleus. At least 30 germ line missense, nonsense, and deletion mutations, as well as mutations of the BMPR1A promoter have been found to cause JPS.

References

Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet. 1997 May;16(1):64-7

Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998a Dec;5(8):751-6

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. 1998b May;62(5):1129-36

Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, Sistonen P, Tomlinson IP, Houlston RS, Bevan S, Mitros FA, Stone EM, Aaltonen LA. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science. 1998c May 15;280(5366):1086-8

Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, Petersen GM, Velculescu VE, Traverso G, Vogelstein B. Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet. 2001 Jun;28(2):184-7

Friedl W, Uhlhaas S, Schulmann K, Stolte M, Loff S, Back W, Mangold E, Stern M, Knaebel HP, Sutter C, Weber RG, Pistorius S, Burger B, Propping P. Juvenile polyposis: massive gastric polyposis is more common in MADH4 mutation carriers than in BMPR1A mutation carriers. Hum Genet. 2002 Jul;111(1):108-11

Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis

and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet. 2004 Mar 13;363(9412):852-9

Delnatte C, Sanlaville D, Mougenot JF, Vermeesch JR, Houdayer C, Blois MC, Genevieve D, Goulet O, Fryns JP, Jaubert F, Vekemans M, Lyonnet S, Romana S, Eng C, Stoppa-Lyonnet D. Contiguous gene deletion within chromosome arm 10q is associated with juvenile polyposis of infancy, reflecting cooperation between the BMPR1A and PTEN tumor-suppressor genes. Am J Hum Genet. 2006 Jun;78(6):1066-74

Aretz S, Stienen D, Uhlhaas S, Stolte M, Entius MM, Loff S, Back W, Kaufmann A, Keller KM, Blaas SH, Siebert R, Vogt S, Spranger S, Holinski-Feder E, Sunde L, Propping P, Friedl W. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007 Nov;44(11):702-9

Calva D, Howe JR. Hamartomatous polyposis syndromes. Surg Clin North Am. 2008 Aug;88(4):779-817, vii

Calva-Cerqueira D, Chinnathambi S, Pechman B, Bair J, Larsen-Haidle J, Howe JR. The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet. 2009 Jan;75(1):79-85

Calva-Cerqueira D, Dahdaleh FS, Woodfield G, Chinnathambi S, Nagy PL, Larsen-Haidle J, Weigel RJ, Howe JR. Discovery of the BMPR1A promoter and germline mutations that cause juvenile polyposis. Hum Mol Genet. 2010 Dec 1;19(23):4654-62

Calva D, Dahdaleh FS, Woodfield G, Weigel RJ, Carr JC, Chinnathambi S, Howe JR. Discovery of SMAD4 promoters, transcription factor binding sites and deletions in juvenile polyposis patients. Nucleic Acids Res. 2011 Jul;39(13):5369-78

Dahdaleh FS, Carr JC, Calva D, Howe JR. Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23. Clin Genet. 2012 Feb;81(2):110-6

Heldin CH, Moustakas A. Role of Smads in TGFβ signaling. Cell Tissue Res. 2012 Jan;347(1):21-36

Latchford AR, Neale K, Phillips RK, Clark SK. Juvenile polyposis syndrome: a study of genotype, phenotype, and long-term outcome. Dis Colon Rectum. 2012 Oct;55(10):1038-43

O'Malley M, LaGuardia L, Kalady MF, Parambil J, Heald B, Eng C, Church J, Burke CA. The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. Dis Colon Rectum. 2012 Aug;55(8):886-92

Howe JR, Dahdaleh FS, Carr JC, Wang D, Sherman SK, Howe JR. BMPR1A mutations in juvenile polyposis affect cellular localization. J Surg Res. 2013 Feb 1;

This article should be referenced as such:

Sherman SK, Howe JR. Familial Juvenile Polyposis Syndrome. Atlas Genet Cytogenet Oncol Haematol. 2013; 17(11):788-790.