Familial Juvenile Polyposis Syndrome

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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.
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**

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**


This article should be referenced as such: