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Juvenile Polyposis Syndrome (JPS): *SMAD4* Mutations

Juvenile polyposis syndrome (JPS) is characterized by predisposition to hamartomatous polyps in the gastrointestinal (GI) tract. The term "juvenile" refers to the type of polyp rather than to the age of onset of polyps. Most juvenile polyps are benign; however, malignant transformation can occur. If polyps are left untreated, they may cause bleeding and anemia. Risk for GI cancers in families with JPS ranges from 9% to 50%.[1,2] A combined syndrome of JPS and Hereditary Hemorrhagic Telangiectasia (HHT) (termed JPS/HHT) is present in most individuals with an *SMAD4* pathogenic mutation.[1]

Cancer Risks and General Management Recommendations

Cancer Type	*SMAD4* Mutation Carrier Lifetime Cancer Risks[1]	General Population Lifetime Cancer Risks	Surveillance/Management Recommendations[3]
Colon	40-50%	4.2%	*Surveillance* • Colonoscopy beginning at age 15 years. Repeat annually if polyps found. If no polyps found, repeat every 2-3 years
Gastric	21%, if multiple polyps present	<1%	*Surveillance* • Upper endoscopy beginning at age 15 years. Repeat annually if polyps found. If no polyps found, repeat every 2-3 years *Surgery* • There may be management issues related to anemia from giant confluent polyps. If anemia develops requiring blood transfusion due to numerous stomach polyps, gastrectomy can be considered in severe cases.
Small Intestine	Increased	<1%	*Surveillance* • No consensus management guidelines
Pancreas	Increased	1.6%	*Surveillance* • No consensus management guidelines • Pancreatic cancer surveillance may be considered on an individual basis. Individuals may consider annual abdominal MRI, annual endoscopic ultrasound (EUS), or enrolling in research protocols to evaluate screening modalities for pancreatic cancer.

Hereditary Hemorrhagic Telangiectasia (HHT):

- Individuals with *SMAD4* mutations are at increased risk for a separate genetic syndrome, hereditary hemorrhagic telangiectasia (HHT). HHT is characterized by an increased risk for vascular malformations and bleeding. Individuals with a *SMAD4* mutation should undergo routine surveillance for HHT-associated vascular lesions within the first 6 months of life or at time of diagnosis. Head MRI to assess for cerebral AVMs should be performed as early as possible, preferably in the first year of life. Contrast echocardiography for detection of pulmonary shunting and AVM should also be performed. Ultrasound or CT examination of the liver to assess for hepatic AVM should be considered if the individual has symptoms such as high-output failure associated with hepatic vascular abnormalities or in the case of otherwise unexplained elevations in liver function tests.
- Individuals with HHT should undergo routine surveillance including annual evaluation by a provider familiar with HHT, periodic hematocrit/hemoglobin and ferritin determination with appropriate treatment for iron deficiency anemia, reevaluation for pulmonary AVM at approximately five year intervals, pulse oximetry in the supine and sitting positions every 1-2 years during childhood, and appropriate pregnancy precautions.[3,4]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *SMAD4* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- An estimated two thirds (~67%) of *SMAD4* mutations occur *de novo* (i.e., a spontaneous mutation not inherited from either parent).[1]
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks, including reproductive risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Larsen Haidle J HJ. Juvenile Polyposis Syndrome. In: Adam MP AH, Pagon RA, et al., ed. *GeneReviews®.* University of Washington; 2017.
2. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Annals of surgical oncology.* 1998;5(8):751-756.
3. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Colorectal. Version 3.2019. 2019.
4. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *Journal of medical genetics.* 2011;48(2):73-87.