

Hereditary Polyposis Syndromes

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Overview of polyposis conditions

Colorectal polyps can be quite common in the general population and most often are not linked to a hereditary polyposis syndrome. Polyps are growths in the colon that could have the potential to become a cancer. Compared to the general population, individuals with a hereditary polyposis syndrome typically have higher numbers of polyps, develop them at younger ages, and often develop them more quickly. The suspicion for a specific polyposis syndrome is based on the amount of polyps, the location of these polyps, and the specific type of polyps found in an individual. There are several main types of polyps that can be seen: adenomas, or adenomatous polyps; hyperplastic polyps; serrated polyps; and hamartomatous or juvenile polyps (the term “juvenile” does not refer to the age of the individual).

There are different hereditary polyposis syndromes currently known. Some of these include:

Familial Adenomatous Polyposis (FAP)

Familial adenomatous polyposis (FAP) is caused by mutations in the *APC* gene. Individuals with classic FAP develop hundreds to thousands of colon adenomatous polyps, typically starting in their teens or twenties. If untreated, virtually all individuals with classic FAP will go on to develop colon cancer. Additional findings include:

- Desmoid tumors (benign tumors, often in the abdominal region)
- Osteomas (bony tumors, particularly of the skull and jaw bone)
- A benign eye finding called Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)
- Upper gastrointestinal tumors
- Benign skin lesions (particularly epidermoid cyst)
- Cribriform-Morular papillary thyroid cancer
- Medulloblastoma brain tumor

There is also an ‘attenuated’ type (or milder form) of FAP that is generally associated with fewer colon polyps (>10 to <100), later ages of onset of colon polyps and cancer. Individuals with the attenuated form of FAP may not start to develop polyps until their 40's to 50's. In general, those with this milder form of FAP have more than 20 polyps, but often fewer than 100. Attenuated FAP is less commonly associated with the above additional findings.

MUTYH-Associated Polyposis (MAP)

There is another similar polyposis condition called *MUTYH*-associated polyposis (MAP). MAP is caused by inheriting **two** mutations in the *MUTYH* gene. Individuals with MAP may have a wide range of polyps but most often they have a milder form of polyposis that is generally associated with fewer colon polyps (>10 to <100) and have later ages of onset of colon polyps (40s-50s) compared with more other forms of familial polyposis, such as classic FAP. Polyps are typically adenomatous, however, other types of polyps can also occur. If untreated, individuals with MAP have a 43% to almost 100% risk to develop colorectal cancer in their lifetimes. Individuals with MAP may also have an increased risk for small intestinal cancer and may present with additional findings including stomach and small intestinal polyps.

Juvenile Polyposis syndrome

Juvenile polyposis syndrome (JPS) is a polyposis syndrome caused by mutations in the *SMAD4* gene or the *BMPR1A* gene. JPS is characterized by the development of multiple juvenile polyps in the gastrointestinal (GI) tract; specifically, in the colon, small intestine, stomach and rectum. These polyps are called 'juvenile polyps' because of their specific appearance under the microscope, and not because of the age of onset in the affected person. However, most people with JPS will develop polyps by the age of 20. Some family members have only 4-5 polyps while others may have > 100 polyps. If the polyps are not removed, they can cause problems, such as an intestinal blockage. The polyps can also develop into cancer. The lifetime risk of colon cancer in people with JPS is up to 50%. The lifetime risk of stomach cancer is ~15-21%, and of any gastrointestinal cancer is ~46-55%. However, with early and close surveillance and polyp removal, the goal is to reduce these lifetime cancer risks.

Serrated Polyposis Syndrome

Serrated Polyposis Syndrome (SPS) is characterized by the presence of multiple serrated polyps found throughout the colon. There is no single gene known to cause SPS at this time. Therefore, a diagnosis is currently based on clinical criteria rather than results of genetic testing.

Serrated Polyposis Syndrome criteria as defined by the World Health Organization (WHO) includes the presence of at least one of the following:

- 1) 5 or more serrated polyps located in before the rectum, all being ≥ 5 mm and with at least 2 being ≥ 10 mm in size; OR
- 2) More than 20 serrated polyps of any size distributed throughout the colon, with ≥ 5 located before the rectum

A person with Serrated Polyposis Syndrome has an increased risk of colorectal cancer, although the exact lifetime risk is unknown. First-degree relatives of someone with serrated polyposis syndrome have an increased risk of colorectal cancer that is 2-3 times the general population risk.

Other polyposis conditions

Clinical testing has recently become available for several other genes that are associated with hereditary polyposis conditions, including *POLE*, *POLD1*, and *GREM1*. Current data suggest that individuals with mutations in these genes have an increased risk primarily for colon polyps and colon cancer, however, we are still learning about these genes and additional information will likely be available in the future. In addition, there are also rarer hereditary cancer conditions, such as Peutz-Jeghers syndrome (*STK11* gene), that are associated with other polyp types.

Testing considerations

Mutations in most of the genes associated with polyposis conditions are passed down in families in an autosomal dominant pattern of inheritance. This means that an individual who carries a mutation has a 50% chance of passing the mutation on to each of their children. It also means that siblings of an individual who carries a mutation have a 50% chance of having the same mutation. MAP, however, is passed down in families in an autosomal recessive pattern of inheritance. This means that an individual carries two mutations, one from each parent.

Often genetic testing is performed by testing a panel of genes, which can include testing for mutations in the genes related to polyposis conditions as well as in additional genes related to other hereditary cancer syndromes. There are benefits, risks, and limitations of panel testing including the lack of data on many of the

additional genes. Some of these genes have not been studied as long or as well, and information about associated cancer risks and screening recommendations will likely change over time.

Individuals who learn they have a polyposis condition, or a mutation in other hereditary cancer genes, are offered special surveillance and risk reduction options.

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