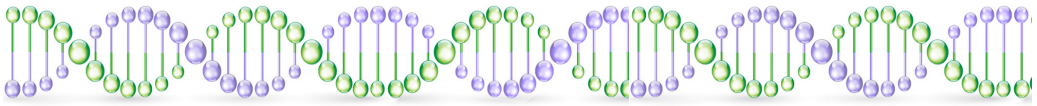
Information Sheet



MUTYH Associated Polyposis syndrome and the MUTYH gene

MUTYH Associated Polyposis (MAP) syndrome affects 1 in 10,000 to 40,000 people. It is more common in people with European ancestry affecting 1 in 5,000 to 1 in 10,000 of this population.

The MUTYH gene makes a type of DNA spellchecker involved in DNA repair. It's called base excision repair. When this spellchecker isn't working, mistakes build up faster in dividing cells and these mistakes increase the risk of growths and cancers. Cancers that develop may show a characteristic pattern of mistakes called microsatellite instability (MSI-H) and may also show loss of staining for the proteins associated with Lynch syndrome on immunohistochemical mismatch repair (MMR IHC) testing.

MUTYH associated polyposis (MAP) results in a high risk of polyps and cancers affecting the stomach, small bowel and colon. This syndrome occurs ONLY if an individual inherits mutations (pathogenic variants) in the MUTYH gene from both their mother and their father (biallelic inheritance; also known as an autosomal recessive condition).

What are MUTYH Founder mutations

Some genetic changes are more common in certain groups of people than others. These mutations are referred to as "Founder Mutations". They occur when people with the same background remain in a separate group due to religious, cultural or geographic reasons.

Two MUTYH mutations are present in 0.2 to 1.14% of people of European descent. These are MUTYH c.452A>G (p.Tyr151Cys), or Y179C for short, and MUTYH c.1103G>A (p.Gly368Asp), or G396D for short. Research has shown that these mutations occurred 7 to 11 thousand years ago and have been passed down from parent to child since then.

How is MUTYH Associated Polyposis syndrome managed?

An individual with MAP may develop 10, 20 or even 100s polyps in their gastrointestinal tract. These polyps, if not removed, can become a cancer. To reduce this risk, colonoscopy (screening of the large bowel) should start at age 20 and gastroscopy (screening for polyps in the stomach or the beginning of the small bowel) starts at age 25. If no polyps are detected, the screening is repeated every 2 years and if polyps are detected, the screening is done every year.

In some cases, there may be so many polyps that they cannot be safely removed using colonoscopy. In these rare cases, removal of all or part of the colon (colectomy) may be required to reduce the risk.

In the absence of screening, someone with MUTYH Associated Polyposis syndrome has an 80% chance of developing colon cancer over their lifetime. With screening, the risk may be very low, even zero.

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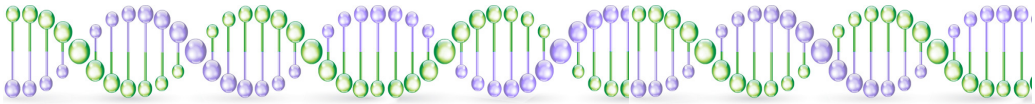

What if you carry only one MUTYH mutation?
This is called being a monoallelic or heterozygous mutation carrier. Published data, including an Australian study, has shown that there is small increase in the lifetime risk of colon cancer (1.15 fold or 2 fold if there is a family history of colon cancer). That is, the risk may increase from the population average of 8% lifetime to 9% (or even 16% lifetime if there is a family history of colon cancer). These families may wish to start bowel cancer screening with colonoscopies at a younger age.

There is no no clinically significant increase in other cancer risk for monoallelic MUTYH mutation carriers. Specifically, the Australian study found an 11% lifetime risk for breast cancer (compared to the average risk of 10 to 15%) and 3% lifetime risk for endometrial cancer (compared to the average risk of 2 to 3%).

Is MUTYH Associated Polyposis syndrome inherited?
Yes. MUTYH Associated Polyposis syndrome is a hereditary cancer syndrome caused by inheriting 2 MUTYH mutations, one from each parent.

Someone who carries a MUTYH mutation, whether male or female, has a 50% chance of passing the mutation on to their daughter or their son.

Someone who has MUTYH Associated Polyposis syndrome has 2 MUTYH mutations will, therefore, always pass one of them on to their children. However, the children will only have MAP if they inherit a second MUTYH mutation from their other parent.

If you have MUTYH Associated Polyposis syndrome, then your siblings (brothers/sisters) have a 25% chance of also having inherited both pathogenic variants and have a 50% chance of having inherited one MUTYH mutation (and, a 25% of not having inherited any).

Who Should Have Genetic Testing for MUTYH Associated Polyposis syndrome?
Medicare funded genetic testing is available if someone has adenomatous polyposis and a 10% chance of carrying a MUTYH mutation based on their personal or family history. Genetic testing should be considered if an individual has:

- a total of 10 or more adenomatous polyps in the colon before age 30
- a total of 10 or more adenomatous polyps in the colon and a colon cancer
- a total of 20 or more adenomatous polyps in the colon before age 60
- a total of 10 or more adenomatous polyps in the colon and brothers and sisters who have also had adenomatous polyps

Predictive testing, when a MUTYH mutation has been detected in a blood relative, is also Medicare funded for at risk adult relatives.

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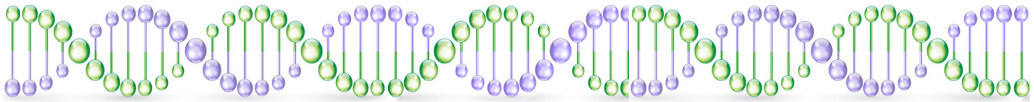

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Genetic testing in suspected MUTYH Associated Polyposis syndrome is often performed via a panel of multiple polyposis-causing genes including:

- the APC gene, particularly if there are lots of polyps
- the Lynch syndrome genes MLH1, MSH2, MSH6 and PMS2, particularly if there is loss of staining on IHC testing
- the Polymerase Proofreading genes POLE and POLD1
- the GREM1 gene, especially if there are other types of polyps

Does this sound like you or your family?
Have you had multiple adenomatous polyps and/or a young onset colorectal cancer? Has an MUTYH mutation been detected in a blood relative? Genetic testing is available.

Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- There are no specific support groups for MUTYH Associated polyposis syndrome in Australia. However, FAP Gene Support Group is based in the UK and has good resources
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about the MUTYH gene and the MAP syndrome.

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