

***NTHL1* Mutations**

What You Should Know About *NTHL1*-Associated Polyposis (NAP) Syndrome

Individuals who inherit two *NTHL1* mutations, one from each parent (i.e., biallelic mutations), have a condition *NTHL1*-Associated Polyposis (NAP) syndrome. This means they are at risk to develop numerous colorectal polyps, which can become cancerous if left untreated. Individuals who have just one *NTHL1* mutation (i.e., monoallelic or heterozygous mutation), do NOT have NAP syndrome, and are instead referred to as carriers. Carriers are not known to exhibit features of NAP but can potentially have children who are affected.

Cancer Risks Associated with *NTHL1* Mutations

Individuals with two *NTHL1* mutations have an increased risk to develop polyps in the colon, which can develop into cancer. The specific lifetime risks of these cancers are currently unknown but are thought to be increased over the general population. Although data are limited, some individuals with NAP have developed cancers of the breast, skin, uterus, prostate, bladder, pancreas, or small bowel.

The Risks to Family Members

NAP syndrome is caused by mutations in the *NTHL1* gene. NAP syndrome is inherited in an autosomal recessive fashion, meaning that a person must inherit a mutation in the *NTHL1* gene from both of their parents to have NAP syndrome. Brothers and sisters of a person with NAP have a 25% (1 in 4) risk to inherit NAP syndrome, a 50% (1 in 2) risk to have one *NTHL1* mutation, and a 25% (1 in 4) chance that they will not have an *NTHL1* mutation. It is important to know that individuals with one *NTHL1* mutation have an increased risk for having a child with NAP syndrome, and their spouse should be offered testing to see if they also have an *NTHL1* mutation.

Managing the Risks

Recommendations for managing these risks may include:

- Begin colonoscopy at age 25-30 years. Continue every 2-3 years if negative
- If polyps are found, colonoscopy every 1-2 years with consideration of surgery if the number of polyps becomes unmanageable by colonoscopy
- Consider surgical evaluation if appropriate
- Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the number and progression of adenomas

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