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Monoallelic/Heterozygous *MSH3* Mutations

Individuals who inherit two *MSH3* mutations (i.e., biallelic mutations), one from each parent, have *MSH3*-associated polyposis, and may develop numerous colorectal and intestinal polyps, which can become cancerous if left untreated.

Individuals who have one *MSH3* mutation (i.e., monoallelic or heterozygous mutations), do NOT have *MSH3*-associated polyposis, and are instead referred to as carriers. Carriers are not known to exhibit features of *MSH3*-associated polyposis, but can potentially have children who are affected.

Currently, there are limited data regarding cancer risks in individuals with a monoallelic *MSH3* mutation. Additionally, there are no consensus guidelines for modified management for individuals with a monoallelic *MSH3* mutation. Cancer surveillance and management should be based on personal risk factors and family history.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *MSH3* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Individuals who inherit two *MSH3* mutations, one from each parent, are at risk to develop *MSH3*-associated polyposis. If both parents are carriers of an *MSH3* mutation, each of their children has a 25% chance to have *MSH3*-associated polyposis.
    - *MSH3*-associated polyposis is characterized by adult-onset polyps (adenomas) in the colon and small intestine that can progress to cancer if untreated. These individuals may also be at increased risk for stomach cancer and brain tumors.
- 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. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Adam R, Spier I, Zhao B, et al. Exome sequencing identifies biallelic *MSH3*germline mutations as a recessive subtype of colorectal adenomatous polyposis. *American Journal of Human Genetics*. 2016;99(2):337-351. doi:10.1016/j.ajhg.2016.06.015.
2. NCCN Clinical Practice Guidelines in Oncology®. Genetic/Familial High-Risk Assessment: Colorectal. V3.2019. 2019.