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Determining Zygosity of Two MUTYH Pathogenic Variants

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Abstract

Biallelic pathogenic variants in the gene MUTYH are associated with MUTYH-associated polyposis syndrome, which is associated with an increased risk for adenomas of the colon and colorectal cancer. Determination of zygosity of MUTYH pathogenic variants is important to determine appropriate screening recommendations and future management. A patient diagnosed with colon cancer was identified with two pathogenic variants in MUTYH, where it could not be determined by the laboratory whether the variants were in cis or in trans. After further testing of family members, it was determined patient has a diagnosis of MUTYH-associated polyposis and her screening greatly differs with colonoscopies every year, instead of at a greater interval with only a diagnosis of colon cancer.

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Introduction

The MUTYH gene is associated with oxidative DNA damage repair [1]. In the presence of biallelic pathogenic variants, an autosomal recessive disorder, MUTYH-associated polyposis (MAP) is present, which is a significantly increased risk for colorectal cancer and adenomas of the colon. Individuals affected with MAP are either homozygotes – identical MUTYH pathogenic variants in each allele or compound heterozygotes – different MUTYH variant in each allele [2].

It is estimated that approximately 1 in 45 individuals carry at least one pathogenic variant in MUTYH [3]. Currently, individuals with MUTYH heterozygous pathogenic variants are not associated with an increased risk for certain cancers, such as colorectal, breast and endometrial [4]. Of individuals diagnosed with colorectal cancer, the rate of biallelic pathogenic variant carriers is <1% [1]. In general, MAP is associated with an increased risk of adenomas of the colon; therefore, regular screening with colonoscopy every 1-2 years is recommended, as long as the adenoma burden can be handled endoscopically [5].

A large number of adenomas in MAP are not always present, as colorectal cancer can occur with very few adenomas, <10 present [2,6,7]. By age 60, there is an approximate 43-63% risk for colorectal cancer [8]. This paper will present a case study of an individual with no previous history of adenomas, who was diagnosed with colon cancer following a routine screening colonoscopy and subsequently diagnosed with MAP.

Case Study

Patient is a 52-year-old asymptomatic Caucasian female, who presented for a routine screening colonoscopy and found to have an invasive moderately differentiated adenocarcinoma of the sigmoid colon. The mass was four centimeters with invasion through the muscularis propria and subserosal adipose tissue. Pathologic staging classification is pT3, N0.

She was also found to have 6 polyps, including tubuloviollous adenomas and tubular adenomas. At the time of her diagnosis, she did not meet NCCN criteria for polyposis testing due to <10 adenomatous polyps nor did she meet lynch syndrome criteria due to diagnosis >50 and no loss of nuclear expression identified in the immunohistochemistry of the tumor. However, updated guidelines provide a category 2B recommendation for consideration for multi-gene panel testing for all individuals diagnosed with colorectal cancer diagnosed > 50 years old [9]. Therefore, patient underwent genetic testing with an 84-gene multi-gene panel test and was found to have two pathogenic variants in MUTYH: c.1187G>A (p.Gly396Asp) and c.700G>A (p.Val234Met).

ClinVar, a database that aggregates information about genetic variations, classifies the p.Gly396Asp variant as "pathogenic/likely pathogenic" through 67 different submissions to the database [10,11]. The p.Val234Met variation has conflicting interpretations through 14 submissions of "pathogenic", "likely pathogenic" and "uncertain significance". Both variants are classified as "pathogenic" by the lab performing the testing. Per the report, the lab was not able to determine whether the MUTYH variants were in cis (on the same chromosome) or in trans (opposite chromosomes); therefore, it could not be determined based on her results the presence of the autosomal recessive disorder, MUTYH-associated polyposis (MAP) syndrome. Since the presence of MAP could affect her future management and screening, it became important to determine zygosity. However, patient was adopted and does not know any biological family information; therefore, parents are not accessible for testing to determine inheritance.

In the absence of MAP, current surveillance guidelines following a diagnosis of colon cancer include a colonoscopy at one year post surgery. If advanced adenoma is present, repeat in one year, if no advanced adenomas are present, repeat colonoscopy in 3 years, then every 5 years [9]. Following the diagnosis of MAP, individuals are followed with colonoscopy and polypectomy every 1-2 years, with consideration for colectomy if adenoma burden cannot be managed endoscopically. It is for this reason, due to the vast differences in long-term follow up for individuals with MAP vs. colon cancer diagnosis alone, it is important to determine patient's zygosity.

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Although biological parents were unavailable for testing, patient has two children, both of whom were willing to be tested. If the variants are in trans, each child will be identified with one pathogenic variant in MUTYH. If the variants are in cis, a child may have two pathogenic variants in MUTYH or none. After testing, one child was identified with the c.700G>A (p.Val234Met) pathogenic variant and the other child was identified with the c.1187G>A (p.Gly396Asp); therefore, confirming the diagnosis of MAP in patient.

Conclusion

The presence of MAP is associated with a significantly increased risk for the development of colorectal cancer and influences the recommendations for long-term screening. In the absence of appropriate surveillance, the risk for colorectal cancer rises to 80-90% [8]. If a patient is diagnosed with MAP following a diagnosis of colon cancer and underwent a segmental resection, annual surveillance colonoscopy is recommended for the remaining colon and rectum, as a metachronous colorectal cancer can occur in 10% of patients on surveillance [6].

Discussion

Although patient did not meet current polyposis criteria or lynch syndrome criteria for genetic testing, multi-gene panel testing was performed due to her diagnosis of colon cancer. Due to the provider ordering genetic testing, two pathogenic variants were identified in MUTYH, which were later to be determined in trans and associated with MAP.

When the zygosity of MUTYH pathogenic variants is in question, it is important to evaluate available family members to assist in determining diagnosis. Without testing the case study's children, it could not be definitively determined whether or not patient had a diagnosis of MAP and may have been followed based solely on her diagnosis of colon cancer; therefore, undergoing colonoscopy at 1 year post colon resection, then in 3 years and repeating every 5 years thereafter. However, due to this determination, patient will have colonoscopies on an annual basis.

Competing Interests

The authors declare that they have no competing interests.

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