C-84

Genetic evaluation following *MUTYH* analysis for European founder variants is critical to identify at-risk patients: a laboratory's experience

Anna Victorine, MS, LCGC; Dagny Noeth, MS, CGC; Mary Hricik, MS; CGC, Elizabeth Lyon, MS, CGC; Alecia Willis, PhD; Melissa Hayden, PhD
Center for Molecular Biology and Pathology, Laboratory Corporation of America®, Research Triangle Park, North Carolina

I. Introduction

MUTYH-Associated Polyposis syndrome (MAP) is a rare, autosomal recessive predisposition to colon polyposis and colorectal cancer caused by biallelic pathogenic or likely pathogenic (P/LP) variants in the *MUTYH* gene (also known as *MYH*). It is associated with the development of hundreds to thousands of colon polyps over an individual's lifetime and a significantly increased risk of colorectal cancer if polyp burden is not managed. Comprehensive testing of the *MUTYH* gene to evaluate for MAP has been available commercially for over a decade. The two most commonly described *MUTYH* pathogenic variants are the European founder variants (FVs) c.536A>G (Y179C) and c.1187G>A (G396D). These two mutations make up 50-82% of all *MUTYH* mutations in those with a diagnosis of MAP[1]. Recently, direct-to-consumer genetic testing has increased access for the analysis of these two FVs, which will likely increase the number of patients potentially at an increased risk for MAP. Here, we discuss a clinical laboratory's experience with the spectrum of identified variants in the *MUTYH* gene and demonstrate that testing limited to FVs only will not identify many patients at risk for MAP.

II. Methods

A set of 186 consecutive patient results ordered for hereditary cancer panels ranging from 7-27 genes at our laboratory that were identified to carry at least one *MUTYH* variant were retrospectively analyzed. The specific variant(s) and internal classifications were cataloged for each. Clinical information from the requisition form and/or obtained during the prior authorization process was catalogued for cases in which two *MUTYH* variants were identified.

III. Results

- A total of 193 *MUTYH* variants were identified across 186 patient samples. In total, 52 unique variants were detected in the dataset: 17 unique P/LP variants and 35 unique variants of uncertain significance (VUS).
- **Figure 1**: The two European *MUTYH* FVs made up 78.9% of all P/LP variants. The majority of the remainder were less common variants previously described in ClinVar and/or medical literature and two were not previously described in the literature nor ClinVar.
- **Figure 2**: Six patients were identified with two P/LP variants and were presumed to be affected with MAP: three were either compound heterozygous or homozygous for *MUTYH* FVs, one had a single *MUTYH* FV and second less common variant, and two had two less common *MUTYH* variants. No patients were identified to have an *MUTYH* P/LP variant as well as a VUS.
- **Figure 2**: 33% of patients with two *MUTYH* variants had clinical histories not consistent with MAP.

Figure 1. *MUTYH* variants identified

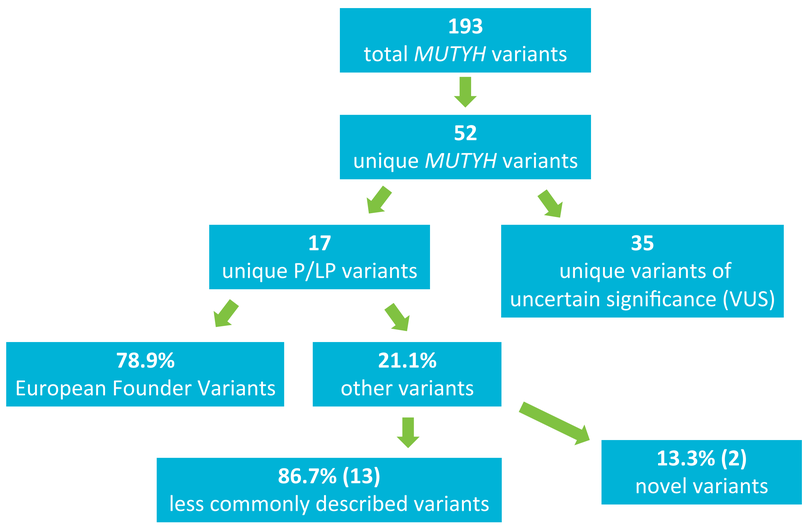
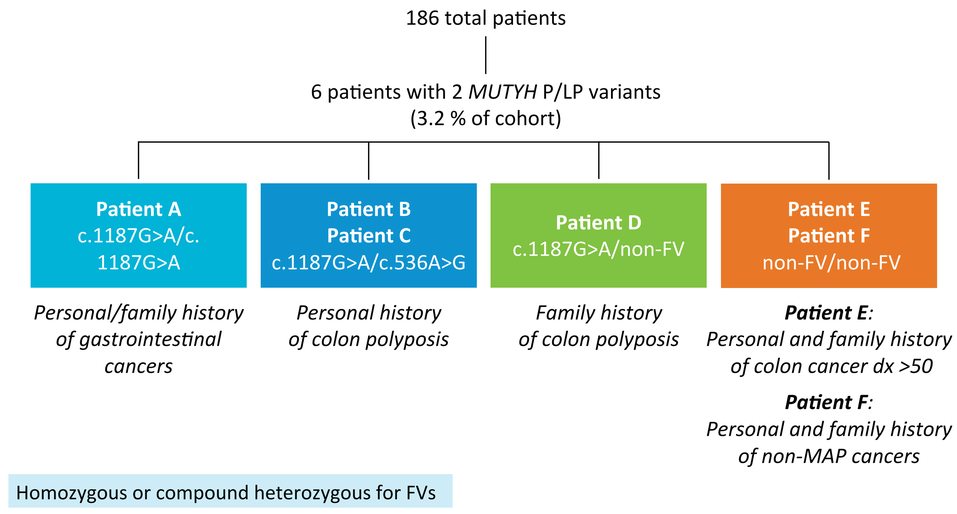


Figure 2. Clinical histories and variant combinations of patients with two *MUTYH* variants



Across all patients identified with two *MUTYH* variants, 33% would not have been identified on a test that only included the two European founder variants.

IV. Conclusions

Across patients identified with two *MUTYH* variants, 33.3% would not have been identified on a test that only included the two European *MUTYH* FVs. This means that a diagnosis of MAP would likely be missed without post-test genetic counseling, evaluation, and/or additional analysis of the *MUTYH* genes. Two patients (**Figure 2**, **Patients E-F**) had personal and family histories inconsistent with MAP; in this situation, a diagnosis of MAP for these patients would both have likely been missed without thorough genetic evaluation and the utilization of panel testing that included sequencing the *MUTYH* gene[2]. An additional patient (**Figure 2**, **Patient D**) with two *MUTYH* variants would have merely been identified as a carrier through only testing for the FVs. In our cohort, this patient did have a family history of colon polyps; if this patient was self-identified on a direct-to-consumer test as carrying an *MUTYH* family variant, follow-up genetic counseling would likely have uncovered the family history of colon polyps and follow-up comprehensive *MUTYH* evaluation would presumably have been offered. These examples illustrate the importance of clinical genetic evaluation and/or genetic counseling for patients who use direct-to-consumer genetic testing to assess their risk for hereditary colorectal cancer predispositions including MAP. These findings and conclusions are also more widely applicable to other conditions in which targeted testing for only specific variants is routinely utilized. Laboratories offering targeted testing for the two *MUTYH* European FVs should regularly encourage patients and providers to follow-up with post-test genetic counseling and evaluation, even in the absence of personal or family history consistent with MAP, to ensure patients are able to maximize the benefit of this testing.

V. References

1. Aretz S et al (2014). MUTYH-associated polyposis (MAP): evidence for the origin of the common European mutations p.Tyr179Cys and p.Gly396Asp by founder events. *Eur J Hum Genetic* 22(7):923-9
2. Sutcliffe E et al (2019). Multi-gene panel testing confirms phenotypic variability in MUTYH-Associated Polyposis. *Fam Cancer* 18(2):203-9.

Poster presented at the *38th NSGC Annual Conference*; 2019 November 5-8; Salt Lake City, UT.