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The co-occurrence of *MUTYH* European founder variants and pathogenic variants in separate genes: one laboratory's experiences and implications for genetic counseling on direct-to-consumer genetic test results

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I. Introduction

The availability of Direct-To-Consumer (DTC) genetic testing has expanded rapidly in recent years, with consumers now electing to learn about common genetic variants impacting cancer risk. Most recently, DTC testing specifically for the two *MUTYH* gene European founder variants (EFVs) became available to consumers in 2019. Here, we present observational data of patients at our laboratory who were found to carry one *MUTYH* EFV as well as a second pathogenic or likely pathogenic (P/LP) variant in a separate gene. We discuss potential implications if these patients had only had genetic testing for the *MUTYH* EFVs as opposed to a multi-gene panel with sequencing and deletion/duplication analysis.

II. Methods

A set of 85 consecutive patients identified to carry one *MUTYH* EFV through Hereditary Cancer Panels (HCP) at our laboratory were retrospectively analyzed. HCPs ranged from 7-27 genes. Patients with two *MUTYH* EFVs were excluded from analysis. The specific variants, internal classifications for each variant, and the clinical information provided were reviewed. Clinical information was compared to societal testing recommendations using the following National Comprehensive Cancer Network (NCCN) guidelines: Genetic/Familial High-Risk Assessment Breast and Ovarian Version 3.2019 (*BRCA1*, *BRCA2*), Genetic/Familial High-Risk Assessment: Colorectal Version 1.2018 (*APC*, *EPCAM*, *MUTYH*), and Gastric Cancer Version 2.2018 (*CDH1*).

III. Results

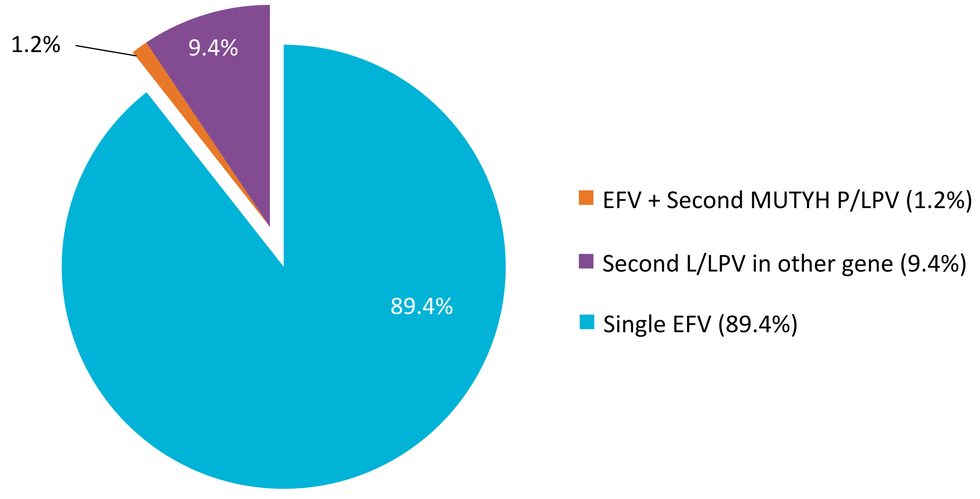
A total of 85 patients were identified with a single *MUTYH* EFV. Of these, eight patients (9.4%) had a second P/LP variant in a separate gene (*EPCAM*, *ATM*, *APC*, *BRCA1*, *BRCA2*, *FANCC*, *NBN*, *CDH1*) and one (1.2%) had a second non-EFV in *MUTYH* (**Figure 1**). Eight of the nine patients had clinical indications consistent with a P/LP variant in the second gene and one had no indication provided (**Table 1**). Of those with a second P/LP variant and clinical indication provided, 75% (n=6) met current NCCN guidelines for testing of the gene. The remaining 25% (n=2) had P/LP variants in genes without current NCCN testing criteria (*ATM*, *FANCC*).

Table 1. Identified variants and clincial histories of patients with a second P/LPV

Patient	*MUTYH* FV	2nd Gene	Variant	Classification	Personal Cancer History	Family Cancer History
1	c.1187G>A	*FANCC*	c.1642C>T	Pathogenic	Colon	**Breast**
2	c.1187G>A	*BRCA2*	c.1929delG	Pathogenic	—	**Breast**, Brain, **BRCA2**
3	c.1187G>A	*EPCAM*	Exon 8-9del	Pathogenic	**Colon**	Breast, **Colon**, **Prostate**
4	c.1187G>A	*ATM*	c.3372C>G	Pathogenic	**Breast**, Uterine, Colon	Colon, **Breast**
5	c.1187G>A	*CDH1*	c.2430delT	Pathogenic	—	Colon, **Gastric**
6	c.1187G>A	*BRCA1*	c.1175_1214del40	Pathogenic	**Ovarian**	**Ovarian**, **Prostate**
7	c.1187G>A	*APC*	c.3927_3931delAAAGA	Pathogenic	**Colon polyps**	**Colon**
8	c.1187G>A	*MUTYH*	c.393G>A	Likely Pathogenic	—	Renal, Peritoneal
9	c.1187G>A	*NBN*	c.1515delG	Likely Pathogenic	*Not provided*	*Not provided*

***Indications in blue are most consistent with 2nd gene**

Figure 1. Patients with one *MUTYH* EFV



IV. Conclusions

Single *MUTYH* EFVs are routinely identified on HCPs. With the recent advent of targeted DTC testing for the *MUTYH* EFVs, incidental detection of these variants is expected to increase and may lead to increased referrals for genetic counseling to determine whether follow-up genetic testing is appropriate. These increased referrals would particularly benefit the population of patients that choose to pursue genetic testing outside of the clinical realm. Our data found that 9.4% of patients identified to carry at least one *MUTYH* EFV on a clinical HCP had a second P/LP variant in a separate gene. If these patients had opted for DTC testing of the *MUTYH* EFVs and had not pursued clinical genetic testing in the form of an HCP, their second variants would have been missed. Given that 75% of our cohort who carried an *MUTYH* EFV and a second P/LP variant in a separate gene met NCCN criteria for testing of the second gene, a referral to genetics to discuss the DTC-identified *MUTYH* EFV has the ability to enhance identification of patients at risk for hereditary cancer syndromes who may otherwise have been missed.

Though carrying two separate cancer predispositions is rare[1], our experience suggests that patients identified to carry an *MUTYH* EFV via a DTC test who have never had clinical genetic counseling should be encouraged to seek out comprehensive genetic evaluation to assess for the likelihood of a second P/LP variant in *MUTYH* as well as other genes that may contribute to their overall cancer risk. HCPs may be an efficient follow-up test to identify additional variants in the *MUTYH* genes (increasing the risk of *MUTYH*-associated polyposis) and address other cancers in the family[2, 3]. Laboratories offering targeted testing for the two *MUTYH* EFVs and providers asked to interpret a patient's DTC results should encourage patients to follow-up with post-test genetic counseling and evaluation and should discuss the possibility of additional underlying cancer predispositions.

V. References

1. Neben et al (2019). Multi-gene panel testing of 23,179 individuals for hereditary cancer risk identifies pathogenic variant carriers missed by current genetic testing guidelines. *J Molec Diag* 21(4):646-657.
2. Willoughby et al (2019). Genetic testing to guide risk-stratified screens for breast cancer. *J Pers Med* 9(1):15.
3. Veldwijk et al (2016). Preferences for genetic testing for colorectal cancer within a population based screening program: a discrete choice experiment. *Eur J Hum Genet* 24(3):361-366.

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