

Background

The simultaneous interrogation of multiple genes through next-generation sequencing technology is being utilized more frequently in hereditary cancer testing. While this has benefits of reducing cost and allowing clinicians to cast a wide net in elucidating the cause for a patient's cancer, panel testing also has the potential to reveal unexpected information. We report on a proband with pathogenic variants in two different hereditary colon cancer syndrome genes that may have been missed by a traditional single gene approach and has significant implications to family members.

Case report

Clinical features:

A 39-year-old male with history of colon cancer diagnosed at 38, with normal IHC, and >20 colon polyps presented for genetic counseling. Family history was significant for a paternal aunt and paternal uncle with colon cancer in their early 50s. Both parents reportedly had colon polyps requiring frequent colonoscopy; his mother had a TAH-BSO at 40 for unknown reasons.

Molecular testing:

Next-generation sequencing of 7 genes – APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2 (high-risk hereditary colorectal cancer panel with deletion/duplication analysis, Invitae, San Francisco, CA) – identified the following variants:

- A homozygous missense variant in exon 13 of MUTYH: c.1187G>A (p.Gly396Asp) classified as Pathogenic
 - This variant is a common cause of MUTYH-associated polyposis in individuals of Northern European ancestry and has been reported to co-segregate with disease in patients with colorectal cancer, FAP, or attenuated FAP (PMID: 11818965, 16557584, 17489848, 19793053).
 - Experimental studies have shown that this missense change disrupts MUTYH protein function (PMID: 15987719, 18534194, 20848659).
- A heterozygous duplication of exon 7 of MSH2 classified as Likely Pathogenic.
 - A similar duplication of exon 7 in the MSH2 gene has been previously reported in a patient affected with colorectal cancer (PMID: 15713769).
 - Given the likelihood that this is an intragenic duplication, it would likely result in a frameshift leading to a premature translational stop signal and an absent or disrupted MSH2 protein.

Family testing:

Due to this finding, the patient's parents were referred for genetic counseling and testing; his mother was found to carry the MSH2 duplication. Both parents are obligate carriers of the MUTYH variant. While testing was pending, his mother was diagnosed with colon cancer.

Discussion

The identification of multiple pathogenic variants in a proband is not an infrequent occurrence in hereditary cancer panel testing. A review of 6852 samples tested using a NGS hereditary cancer panel between January 1, 2014 and April 22, 2015 identified 9 additional probands with multiple pathogenic variants.

Genes	Indication
BRCA1 and CDKN2A	Family history of ovarian, breast, and melanoma
BRCA2 and CHEK2	Breast cancer at 56, personal history of endometrial and skin cancer
BRCA1 and PALB2	Breast cancer at 29 years and family history of cancer
EPCAM and BRCA2	Colorectal cancer diagnosis at 32 and 54 years
ATM and CHEK2	Unilateral breast cancer at 43 years
BRCA1 and BRIP1	Family history of breast cancer
BRCA1 and BRCA2	Ovarian cancer at 40 and unilateral breast cancer at 46 year
MSH2 and PALB2	Colon cancer (age not provided)
BRCA1 and APC	Family history of breast and pancreatic cancer

Six patients had variants in high-risk cancer genes (APC, BRCA1/2, CDKN2A, EPCAM, PALB2), two patients had a variant in a high-risk and moderate-risk gene (BRCA1/2, BRIP1, CHEK2), and one patient had variants in moderate-risk genes (ATM, CHEK2).

Although the cancer risk in individuals who carry multiple pathogenic variants has not been established for different combinations of genes, the identification of multiple pathogenic variants does allow for screening for cancers associated with each gene separately and has implications for cancer risk for family members.

In particular, this may have a significant impact on family members who test negative for a known familial pathogenic variant yet could still be at risk for cancer due to a second pathogenic variant in a family.

Conclusion

The findings in this report demonstrate an additional utility of multi-gene hereditary cancer panel testing and illustrate the importance and implications of testing family members in the context of identifying pathogenic variants in more than one hereditary cancer syndrome.

Pedigree:

